Lymphatic malformations (LMs), traditionally called lymphangiomas, are localized areas of abnormal development of the lymphatic system that occur most commonly in the head and neck region. The precise etiology of LMs still remains unknown. Most investigators believe that they are congenital malformations of the lymphatic vessels or certain acquired factors resulting in lymphatic obstruction, lymph fluid retention, lymphangiectasia and proliferation. The incidence of lymphatic malformations is 1.2–2.8%. They can be found at any age of life, approximately 50% are present at birth and 90% are diagnosed before 2 years of age.1 Both genders are equally affected.2,3 Tongue, lip, buccal mucosa and neck regions are the most commonly affected sites. LMs appear as transparent, red or yellow blisters when involving the mucous membrane. The lesions would grow rapidly with infection, trauma or bleeding. Pathologically, LMs can be divided into two types: macrocystic and microcystic, but mixed (macro- and microcystic) forms are usually present clinically, such as macrocystic lesions in the neck with microcystic lesions in the tongue or cheek. The LMs can be divided into serous and chylous type based on different liquid ingredients in the cysts. The vesicles may be filled with bloody or purulent fluid when accompanied with bleeding or infection. The cyst fluids of LMs may appear in various colors in different sites.4 A staging system was proposed by de Serres et al.5 based on the location and extent of the lesions: stage I is unilateral infrahyoid, stage II is unilateral suprathyroid, stage III is unilateral infrathyroid and suprathyroid, stage IV is bilateral infrathyroid, stage V is bilateral infrathyroid and suprathyroid. This type of staging system does offer some important prognostic implications: generally, as the stage increases, the prognosis becomes poorer.

Although lymphatic malformations are benign lesions, spontaneous regression is rarely seen and only 1.6–16.0% has been reported.6–8 With adequate follow-up, a recurrence is usually followed by a recurrence. The management of head and neck LMs is challenging because of the close association with the adjacent vital structures and poor demarcation. Current treatment methods of LMs include surgery, sclerotherapy and laser therapy, or a combination thereof.9 Surgery used to be the mainstay or even the only treatment choice and still remains the first choice in the hands of many surgeons. However, with technical advancements and...
accumulation of clinical experience in sclerotherapy and laser therapy, many authors agree that the treatment plan of LMs should depend on the primary sites and type of the lesions individually, rather than using surgery as the only effective treatment option.

Based on the published literatures and clinical experiences, we established the treatment guideline in order to provide a protocol for the management of head and neck lymphatic malformations. This protocol will be reviewed and updated periodically to include and reflect cutting edge knowledge to provide the best treatment modalities to benefit our patients.

Clinical and histopathological features

Most lymphatic malformations appear at birth, but the clinical symptoms often present at older ages. Gross reported that 50–75% can be diagnosed at birth, with 80–90% of the remaining cases diagnosed by the age of 2 years. Infection, trauma or changes in hormone level can result in destruction of lymphatic circulation and expansion of the lesions. Radiation therapy or connective tissue diseases (CTDs) can also aggravate the condition.

More than 70% of lymphatic malformations are found in the head and neck region, which may be related to the rich lymphatic system of this area. The clinical symptoms are generally determined by the lesion size, depth and extent of adjacent fibrosis. Cutaneous or mucosal lesions usually present as liquid-filled vesicles, which may be connected with the subcutaneous or submucosal lymphatic lumens. Deep-seated lymphatic malformations can be divided into diffuse edema (microcystic) and localized multilocular cyst (macrocystic). Macrocystic lymphatic malformations, known as cystic hygroma previously, occur mostly in the neck region and can be resected completely as they are localized, while lesions in the floor of mouth, buccal mucosa and tongue are diffusely infiltrative and microcystic with poor demarcation and thus cannot be extirpated totally.

There are wide variations in the growth rate of LMs. Sudden rapid enlargement often result from infection, trauma or bleeding. Extensive lesions involving the floor of the mouth, oropharynx or neck usually result in airway problems. Cervical malformations may compress the pharynx, mediastinum and trachea, causing breathing difficulties. Laryngeal lesions can completely block the larynx with resultant respiratory compromise resulting in severe tissue defects, leading to cosmetic and functional complications; (2) the lesions are poorly demarcated; (3) the walls of lymphatic vessels of LMs are thin and friable; (4) diffuse LMs often involve important structures such as the cranial nerves or vital blood vessels, making complete resection more difficult; (5) complete resection of the lesions is especially challenging because of the potential complications, such as facial nerve damage, Horner’s syndrome, postoperative lymphatic leakage, seroma and poor wound healing. Emery et al. reported that the incidence of facial palsy after surgical extirpation was 5.9–33%; Hancock et al. demonstrated seromas in 9.8% of wounds in which local drains were used and 3.6% of the wounds in which drains were not used. (6) Tissue defects, heavy bleeding and infection may occur with incidence of 3.1%, 1.6% and 2.5%, respectively, when total excision was performed. Therefore, non-surgical conservative treatments including radiotherapy, electrocoagulation, cryotherapy, ligation, embolization, sclerotherapy and laser therapy have been recommended as a primary or adjunctive treatment for these lesions. Radiotherapy can inhibit the growth of the lesions but has the potential of malignant transformation. Laser therapy is effective for superficial microcystic malformations, but ineffective for deep-seated ones. Sclerotherapy was advocated by Watson and McCarthy early in 1964. Although a multitude of sclerosing agents have been tried including hypertonic glucose solution, ethanol, quinine, doxycycline, sodium morrhuate, bleomycin and OK-432, corticosteroids, etc., bleomycin and OK-432 remain the mainstay therapeutic agents for LMs. Yura et al. first reported intralesional injection of bleomycin and OK-432 for lymphatic malformations with excellent results. Ogita et al. reported that in eight of nine patients treated with OK-432, complete regression of the LM was observed. Sainsbury et al. reported intralesional bleomycin injection of LMs with a 100% overall response rate and 40% complete response rate. Burrows et al. treated 41 patients of LMs by intralesional doxycycline with related response rate about 83%. Curative effect was also achieved with Pongyangmixin, bleomycin A5 produced by Streptomyces pingyangensis in China. Concerns still remain regarding complications with each sclerosing agents. Doxycycline can cause neural damage, OK-432 may be associated with sepsis, shock, myalgia, and bleomycin still carries a warning of pulmonary

Diagnosis and treatment

It is not difficult to make the diagnosis of LMs based on history and clinical manifestations. Lesions in oral mucosa commonly present as microcystic, isolated or multiple sporadic round nodules or punctuate lesions. The lesion is soft in texture and pink to dark red in color scattered with yellow vesicles, sometimes with venous malformations. The most commonly affected areas of deep-seated LMs are the lower 2/3 of the face such as the lip, cheek, tongue and ear, etc., which often cause hypertrophy as well as deformities like macroglossia, macrocheilia and may be associated with mandibular hypertrophy. Localized cystic hygromas are usually found in the neck and submandibular regions. They consist of large spaces filled with fluid resembling swelling under the skin, which may be transparent, red, blue or skin colored. Ultrasound and MRI are important adjunctive diagnostic approaches to identify the location, size and extent of the lesions. Lymphatic malformations are low-flow vascular anomalies, often appearing as multiple cystic spaces. The signal intensity is intermediate on T1-weighted image, hyperintense on T2-weighted image with no enhancement after contrast injection. Sometimes macrocystic malformations with hemorrhage display low signal intensity on T2-weighted image due to hemoglobin degradation.

Treatment modalities

Many treatment methods have been documented in the literature, including surgery, various sclerotherapy and laser therapy. Localized microcystic lesions can be resected completely, but impossible for extensive and diffuse ones, the reasons being: (1) most of them involve the lip, cheek and tongue, complete excision may result in severe tissue defects, leading to cosmetic and functional complications; (2) the lesions are poorly demarcated; (3) the walls of lymphatic vessels of LMs are thin and friable; (4) diffuse LMs often involve important structures such as the cranial nerves or vital blood vessels, making complete resection more difficult; (5) complete resection of the lesions is especially challenging because of the potential complications, such as facial nerve damage, Horner’s syndrome, postoperative lymphatic leakage, seroma and poor wound healing. Emery et al. reported that the incidence of facial palsy after surgical extirpation was 5.9–33%; Hancock et al. demonstrated seromas in 9.8% of wounds in which local drains were used and 3.6% of the wounds in which drains were not used. (6) Tissue defects, heavy bleeding and infection may occur with incidence of 3.1%, 1.6% and 2.5%, respectively, when total excision was performed. Therefore, non-surgical conservative treatments including radiotherapy, electrocoagulation, cryotherapy, ligation, embolization, sclerotherapy and laser therapy have been recommended as a primary or adjunctive treatment for these lesions. Radiotherapy can inhibit the growth of the lesions but has the potential of malignant transformation. Laser therapy is effective for superficial microcystic malformations, but ineffective for deep-seated ones. Sclerotherapy was advocated by Watson and McCarthy early in 1964. Although a multitude of sclerosing agents have been tried including hypertonic glucose solution, ethanol, quinine, doxycycline, sodium morrhuate, bleomycin and OK-432, corticosteroids, etc., bleomycin and OK-432 remain the mainstay therapeutic agents for LMs. Yura et al. first reported intralesional injection of bleomycin and OK-432 for lymphatic malformations with excellent results. Ogita et al. reported that in eight of nine patients treated with OK-432, complete regression of the LM was observed. Sainsbury et al. reported intralesional bleomycin injection of LMs with a 100% overall response rate and 40% complete response rate. Burrows et al. treated 41 patients of LMs by intralesional doxycycline with related response rate about 83%. Curative effect was also achieved with Pongyangmixin, bleomycin A5 produced by Streptomyces pingyangensis in China. Concerns still remain regarding complications with each sclerosing agents. Doxycycline can cause neural damage, OK-432 may be associated with sepsis, shock, myalgia, and bleomycin still carries a warning of pulmonary
fibrosis. Ethanol is an effective sclerosant but has the highest complication rate. The injection of ethanol is painful and may injure nerves.

Choice of treatment methods

The choice of treatment should be individualized and based on several factors such as the hyoid level, bilaterality, age of onset, growth rate, type, depth, extent, anatomical location, potential deformity or dysfunction of LMs. Lesions with severe life-threatening functional impairment should be treated early. When there is no significant functional deficit, treatment can be delayed well past infancy and 18–24 months is available to allow for spontaneous resolution. Localized lymphatic malformations can be treated with surgery, laser therapy or sclerotherapy, usually with excellent results. For diffuse lesions or lesions with cosmetic and functional problems, an individualized treatment plan should be made based on the status of the patient and the technology and expertise available. Most often, a multidisciplinary approach will achieve the best results when well planned and implemented. Treatment choice according to cervical LM laterality (unilateral or bilateral) and relationship to the hyoid bone (infrahyoid or suprathyroid) has been discussed by several investigators. While lesion type, depth, extent, anatomical location are the most important factors that should be considered in choosing treatment modalities. Special consideration should be given when planning sclerotherapy in sensitive areas such as orbit. Injections around the orbit, even with minor extravasation, can cause orbital compartment syndrome, patients should be examined postoperatively by an ophthalmologist. Except for young infants and airway lesions, most patients are discharged home the same day.

Oral mucosal microcystic lymphatic malformations

Intralesional injection of Pingyangmycin

Bleomycin is a cytotoxic antitumor antibiotic that can be administered intralesionally by means of transcutaneous injection and is proving to be an exciting modulator of vascular anomalies. Pingyangmycin (PYM) is a single-component A5 of various components of bleomycin, because of the low cost, safety, and ease of availability, percutaneous intralesional injection of Pingyangmycin has been used more frequently for management of vascular malformations as a single modality or in combination with surgery or laser therapy. It has good effect for LMs located in the tongue, lip, cheek, floor of mouth, palate, etc., which could cure small to medium-sized microcystic LMs through infiltration injection. In order to enhance the sclerosant effect, removing all fluid from within the malformation prior to introducing the sclerosant is the most important technical aspect. Eight milligrams of Pingyangmycin powder is dissolved in 5 mL normal saline with addition of 2 mL 2% lidocaine hydrochloride and 1 mL dexamethasone (5 mg). The dosage per injection is 1 mL/cm² of the lesion as determined by clinical measurement, the maximal dose for one injection is 8 mg, and the total dose should not exceed 40 mg in an adult patient. Injection is performed in the way of infiltration anesthesia, until the surface of the lesion becomes expanded and pale. Multiple injections are needed at different sites for larger or more extensive lesions. After injection, the lesion is compressed for 5 min to prevent bleeding and effusion of the sclerosant. If repeated treatment is required, the appropriate interval is 3–4 weeks. If no response is noted after two injections, other treatment options should be considered rather than repeated injections. A treatment cycle often consists of 3–5 sessions. The dosage for children should be reduced accordingly.

After intralesional injection, very few patients develop low grade fever, loss of appetite and skin rash. Pulmonary fibrosis has never been reported. Acute allergic reaction during injection is rarely encountered, but serious consequences or even death may occur if not managed timely and appropriately. Therefore, detail medical history should be taken and first-aid measures (such as first-aid kit, tracheotomy set and intravenous infusion set, etc.) should be prepared before treatment. Close observation of the patients during injection is crucial. If dysphoria, tachypnea, pale face, weak pulse, mental confusion and hypotension occur, injection should be stopped immediately. Oxygen inhalation, rapid intravenous infusion and administration of anti-allergy and anti-shock drugs should be given without delay. The patients’ vital signs should be monitored. In case of cardiac arrest, cardiac massage, mouth to mouth resuscitation or pressure oxygen mask, injection of adrenaline should be performed immediately.

Injection of OK-432

OK-432, also called picibanil, is a biologic preparation of lyophilized powder containing Streptococcus pyogenes Su strain cells (group A, type 3) treated with benzylpenicillin potassium. The drug is originally used as a non-specific immunostimulant to treat malignant tumors, especially for malignant hydrothorax and ascites. Its good efficacy in infantile LMs was first confirmed by Ogita et al. in 1987. The mechanism of OK-432 remains confined within the malformations after injection and stimulate lymphatic endothelial cells, resulting in obliteration of lymphatic channels with minimal local fibrosis. Skin test of penicillin should be done prior to treatment to rule out allergy. The concentration of OK-432 is 0.1 mg/10 mL. The injection is usually performed from different points and directions until the lesion is expanded, the total amount should not exceed 20 mL. If the lesion is not reduced 3–6 weeks after injection, a second injection can be considered and the dose may be increased to 0.3 mg (30 mL). If additional treatment is required, the appropriate interval is 1–1.5 months.

Almost every patient experiences low grade fever (38–39°C) 6 h after injection, which will be relieved after 2–4 days of medication. Most patients demonstrate local inflammatory reactions such as erythema, slight tenderness and swelling of the lesions for 3–7 days, few patients are at the risk of shock-like symptoms. Oxygen administration, antihistamines and corticosteroids should be ready for those with penicillin allergy.

Laser therapy

Laser therapy has been used to treat superficial lymphatic malformations, especially for patients with localized infection. The advantage of laser therapy is the ease of use, less bleeding, minimal pain, reliable effect and repeatable treatment. Atropine can be used preoperatively to reduce salivary secretion. The wavelength of CO₂ laser is 10,600 nm (far-infrared light) with 0.2 mm spot size and 0–6 W continuous output power. The laser probe should be kept at a distance of 0.5–1 cm from the surface of the lesions during operation. The laser beam should be aligned towards the lesion and gradually cauterize the malformed structures from superficial surface to deep layer. Meanwhile, the carbonized debris can be rubbed off by moist cotton ball layer by layer. Any bleeding point should be compressed and the laser power reduced to coagulate small blood vessels until no obvious bleeding is seen. When the lesions have been completely removed, laser power density should be adjusted to 10–15 W/cm² until the wound surface has coagulated. The treatment area should extend 0.2 cm outward of the lesions to prevent recurrence. The depth of cauterization depends on the vertical extent of the lesions. For small and superficial lesions, a
single session of laser therapy may be enough; but for larger and deeper lesions, the superficial lymphatic vesicles are cauterized initially. 2–5 sessions may be required at an interval of 2 weeks. Antibiotics and mouthwash should be prescribed for 3–7 days duration after treatment. Besides CO2 laser, Nd:YAG laser (wavelength 1064 nm, near infrared light), pulsed dye laser and diode laser can also be used.25

**Combined therapy**

Laser therapy and PYM sclerotherapy can be used alternatively or jointly for superficial microcystic lymphatic malformations of the tongue and oral mucosa. The local tissues may become thicker and harder after several injections. Local injection of triamcinolone acetonide can loosen and soften the tissues making the lesions thinner. It must be addressed that the pharmaceutic effect of triamcinolone acetonide could last 2 months, thus the dosage for children below 2 years old should be less then 10 mg, less than 15 mg for those below 5 years old and less than 20 mg for adults. Overdosage may decrease secretion of steroids and disturb bone development.

Triamcinolone acetonide can be injected in the same way as PYM at a concentration of 100% or 50% depending on the severity of hardness. Repeated injections are often necessary at an interval of 3–4 weeks for 4–5 sessions. The outcome can be evaluated 2–3 months after the final injection.

Localized hyperplastic LMs can be treated with surgery, the residual lesions can be further managed with sclerotherapy and/or laser therapy. CO2 laser therapy is better for macroglossia compared with surgical resection, because the laser beam can gasify and carbolize the lesions from the surface with little impact on lymphatic drainage and the tongue function will be improved, while surgical resection usually results in obstruction of lymphatic drainage, thus recurrence is often inevitable.

**Deep-seated microcystic lymphatic malformations**

Treatment of deep-seated microcystic LMs is still a challenging problem; surgical resection alone usually has a poor outcome, often resulting in secondary deformities. Therefore, surgery is no longer the preferred method for deep-seated microcystic LMs. Intralesional injection of OK-432 or Pingyangmycin has been recommended with excellent result in some patients through repeated injections. For complicated cases, surgical correction may be applied after laser therapy and/or sclerotherapy to improve cosmetics and function.9 Endotracheal intubation is required during sclerotherapy for extensive microcystic LMs involving important structures such as the tongue, floor of mouth, soft palate, parapharyngeal space or upper neck where swelling may result in dyspnea.26 The tube can be removed after the swelling has subsided. Prophylactic tracheotomy should be considered for cases with airway problems to maintain upper airway patency. Dexamethasone is often given to help reduce postoperative swelling.

**Macrocytic lymphatic malformations**

Sclerotherapy with Pingyangmycin or OK-432 is the mainstay of treatment for macrocystic lymphatic malformations, and surgery is usually used as complementary therapy.14,27 The lymphatic fluid in the cystic space should be aspirated as much as possible through 7-gauge needle prior to injection of Pingyangmycin (2 mg/mL) or OK-432. The amount of OK-432 (0.1 mg/10 mL) is the same as the aspirated fluid, not more than 20 mL. Large macrocystic lymphatic malformations localized in the upper neck or floor of mouth can lead to serious problems in breathing and deglutition and emergency surgery is often mandatory. Surgical resection should be as radical as possible in the given anatomic regions. Single macrocystic LMs of the neck have a high cure rate through surgery, while recurrence is common in neonatal patients. The result of surgical extirpation is poor for macrocystic LMs involving the tongue, floor of the mouth, cheek, pharynx or multiple anatomic sites, often with higher complication rates, including facial nerve injury.26 As the cysts are thin walled and fluid-filled spaces, it is judicious to proceed with gentle dissection to avoid tearing the thin wall and minimize recurrence. Any infection should be well controlled before surgery.

Surgery should be performed early in some circumstances, for example, LMs in the orbital cavity and surrounding regions, which often cause disfigurement and diminished vision and early surgical excision (usually subtotal) may alleviate these problems.28 If complete resection is impossible, it is advisable to manage different anatomic areas as individual problems, and a "top down" approach is applied to prevent superior swelling of the untreated zone. Chil-
dren with diffuse cervicofacial disease often require maxillo-mandibular correction due to overgrowth of the maxillofacial bones.

The treatment protocol for complicated, mixed lesions (e.g., lymphatic-venous malformation, lymphatic-capillary malformation, etc.) should be individualized and multidisciplinary dependent on the anatomical location and type of the lesions, in order to achieve the best treatment outcome. Children with diffuse disease are likely to have long-term morbidity, and psychosocial consultation as well as support is mandatory in these children.

Conclusion

A number of treatment methods are available for lymphatic malformations of the head and neck region. Sclerotherapy has been most effective in the management of macrocystic LM. Superficial and localized lesions can be treated with intralesional injection and laser therapy, often with good results. If lesions are too extensive for complete excision, sclerotherapy may be used as the primary treatment of choice or postoperative adjunctive treatment. The use of laser therapy and sclerotherapy is simple and with little side reactions. Resection of LMs can be associated with significant morbidity: major blood loss, iatrogenic injury and deformity.

A flowchart of treatment of LMs of the head and neck was illustrated in Fig. 1.

Conflict of interest statement

None declared.

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