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Techniques in Vascular and Interventional Radiology

Common (Cystic) Lymphatic Malformations: Current Knowledge and Management

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The approach to treating common (cystic) lymphatic malformations (LMs) has evolved significantly over the last decade due to clinical research and recent developments in molecular biology. Surgery, sclerosing agents, and medical drugs with specific targets for biological therapy have been reported for the management of LMs. We will discuss the importance to standardize the location and imaging characterization of LMs to improve the knowledge about the outcome of the different therapeutic options. Our goal is to help the reader understand the different options for the management of LMs with the balance between risk and benefit for the patients.
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Introduction

In the updated classification of the International Society for the Study of Vascular Anomalies (ISSVA), the vascular malformations are divided into 4 groups: simple vascular malformations, combined vascular malformations, malformations of major named vessels, and malformations associated with other anomalies. Simple vascular malformations are mainly composed of only 1 type of vessel (capillaries, lymphatics, or veins), except for arteriovenous malformations, which contain arteries, veins, and capillaries.[1]

Common (cystic) lymphatic malformations (LMs) represent a category in the spectrum of simple vascular malformations. Cystic LMs result from sequestered lymphatic sacs that failed to fuse with peripheral draining channels.[2] LMs are classified into 3 morphologic types: macrocystic, microcystic, and mixed cystic consisting of a combination of macrocystic and microcystic types. Churchill et al[3] and Acevedo et al[4] published systematic reviews on the efficacy of different sclerosing agents for the treatment of LMs. Overall, good (>50% decrease in the size of the lesion) or excellent (>90% decrease in the size of the lesion) responses were estimated at 74%[4] and 72.7%.[3] Churchill et al and Acevedo et al mentioned that it is not possible to ascertain whether one agent is more effective than the other. However, most of the authors who published their experience with sclerosing agents (ie, OK-432, Bleomycin, doxycycline, fibrin sealant, polidocanol 1%, alcoholic solution of zein (or Ethibloc), hypertonic saline, acetic acid) mentioned a better response with macrocystic than microcystic, with similar rates of response.

The major problem is the standardization of the location, the size, the architecture, the technique of injection, the definition of response and follow-up to optimize the therapeutic decision, the prognostic estimation and to compare the treatment results. After reviewing the literature and based on our long experience in managing patients with simple LMs, we will discuss the clinical and imaging work-up and follow-up to improve standardization for the benefit of our patients. Also, the different techniques and sclerosing agents' options will be discussed.

Pathology, Epidemiology, and Classification

LMs are benign vascular malformations of the lymphatic system made up of dilated lymphatic channels or cysts lined by endothelial cells with a lymphatic phenotype.

The incidence of LMs varies from about 1 in 6000 to 1 in 16,000 live births with no racial or sexual predilection.[4] LMs are located primarily in the head and neck, accounting for 75%,[3] but they can occur in any part of the body.

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Approximatively half of LMs are detected at birth, with 80%-90% detected by the age of 2.[4] Most of the LMs present as a soft tissue mass with normal overlying skin. However, in some patients, LMs appear suddenly after an intralesional bleeding or infection. In those cases, the clinical presentation is a firm lesion with bluish overlying skin color. The microcystic type presents clinically as a firm lesion with variable skin texture changes, cutaneous vesicles, discoloration, and hyperkeratosis. The clinical staging system proposed by de Serres et al[5] for the head and neck LMs is based on the location and the extent of disease. The following 5 stages are recognized: stage I, unilateral infrahyoid disease; stage II, unilateral suprahyoid disease; stage III, unilateral suprahyoid and infrahyoid disease; stage IV, bilateral suprahyoid disease; and stage V, bilateral suprahyoid and infrahyoid disease. Wiegand et al[6] introduced a staging for LMs of the tongue from I-IV: I—isolated superficial microcystic LMs of the tongue; II—LMs affecting the tongue with muscle involvement (IIa: part of the tongue; IIb: entire tongue); III—LMs affecting the floor of the mouth; IV—extensive microcystic LMs involving the tongue, floor of the mouth, and further cervical structures.

These classifications must be used for the standardization of the patients adding to the clinical history of infection, bleeding, and skin lesions for the management and outcomes of patients with head and neck LMs.

Genetic/Pathogenesis

The pathogenesis is not well understood. The failure of embryonic lymphatic system to communicate with the venous system and an abnormal or insufficient network within the lymphatic system are 2 proposed hypotheses.[7,8] However, more recent research suggests that LMs are not the result of a disrupted vasculogenesis but arise from sporadic genetic abnormalities in specific cells.[9] We have limited evidence of familial inheritance; LMs seem to be multifactorial with somatic or germline mosaic mutations. The sporadic occurrence of LMs suggests somatic mutations as a cause of LMs.[10] The PIK3CA mutations, which encode the catalytic subunit of the PIK3 enzyme, have been found in 94% of patients with LMs.[11] It is unknown if PIK3CA mutations alone can produce LMs. These mutations are commonly found in cancer but not in normal lymphatic channel.[12] To find the pathogenic mutation, a sample of tissue for genetic testing is required because this mutation is not necessarily present in blood.

The mTOR/PIK3 pathway and the vascular endothelial growth factor (VEGF) are involved in the angiogenesis and lymphangiogenesis.[13] The mTOR protein has a central role in the complex intracellular signaling pathway involved in processes such as cell growth, cell proliferation, angiogenesis cellular metabolism, autophagy, and apoptosis.[14] Insulin, growth factor, and hormones can activate the mTOR complex.[15]

Histochemical markers identifying the lymphatic endothelial cells are Podoplanin (D2-40) and lymphatic vessels endothelial hyaluronan receptor (LYVE-1). TLR-4 expression on monocytes is reported as a predictive parameter for the response to OK-432 in LMs.[16,17]

Imaging

Imaging is essential for the diagnosis and to define the architecture and the extension of LMs and the relationship with adjacent structures. The size of the cyst determines the types of LMs: type 1 = macrocystic: ≥1 cm (Fig. 1), type 2 = mixed (macro and microcysts), and type 3 = microcystic: <1 cm. The outcome of mixed cystic LMs and microcystic LMs is different because the architectures are different depending on the percentage of macrocyst vs microcyst components. We propose to improve this classification to allow a better stratification of the mixed LMs type 2 and split the mixed category as follows: mixed LMs type 2a (more than 70% of the cysts are ≥1 cm), mixed LMs type 2b (between 40% and 70% of the cysts are ≥1 cm), and mixed LMs type 2c (less than 40% of the cysts are ≥1 cm with or without a solid matrix) (Fig. 2). Microcystic must be reserved to cysts <1 cm or invisible in a background of solid and ill-defined matrix (Fig. 3). A new classification was proposed by Malic et al[18] for the microcystic LMs. They divided it into 3 types: (1) open-cell microcystic LMs (<2 cm), meaning open connection between the cysts; 2) closed-cell microcystic LMs, meaning no open communication between cysts and lymphatic channels; and (3) channel-like ectatic structure of lymphatic vessels.

On ultrasound, macrocystic LMs consist of hypoechoic or anechoic multiloculated cystic spaces that are separated by thin septa. Sometimes, a fluid level or debris can be observed in cyst, which may result from hemorrhage or infection with a high content of protein and with a varying degree of

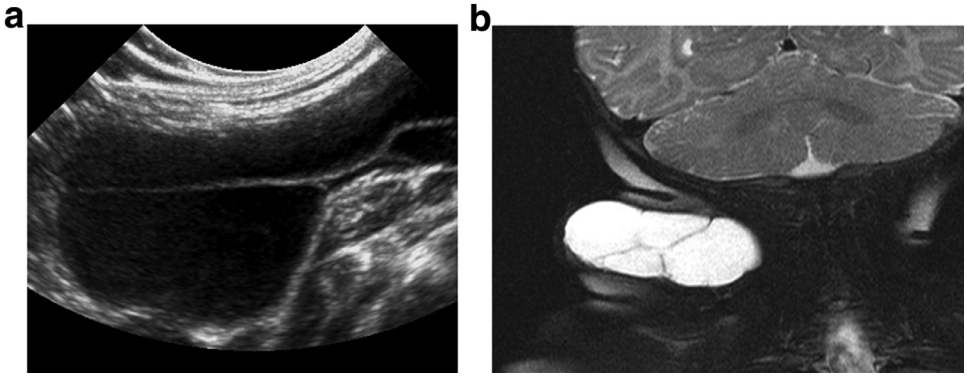

Figure 1 (a, b) Type 1 macrocystic LM: cysts ≥1 cm.

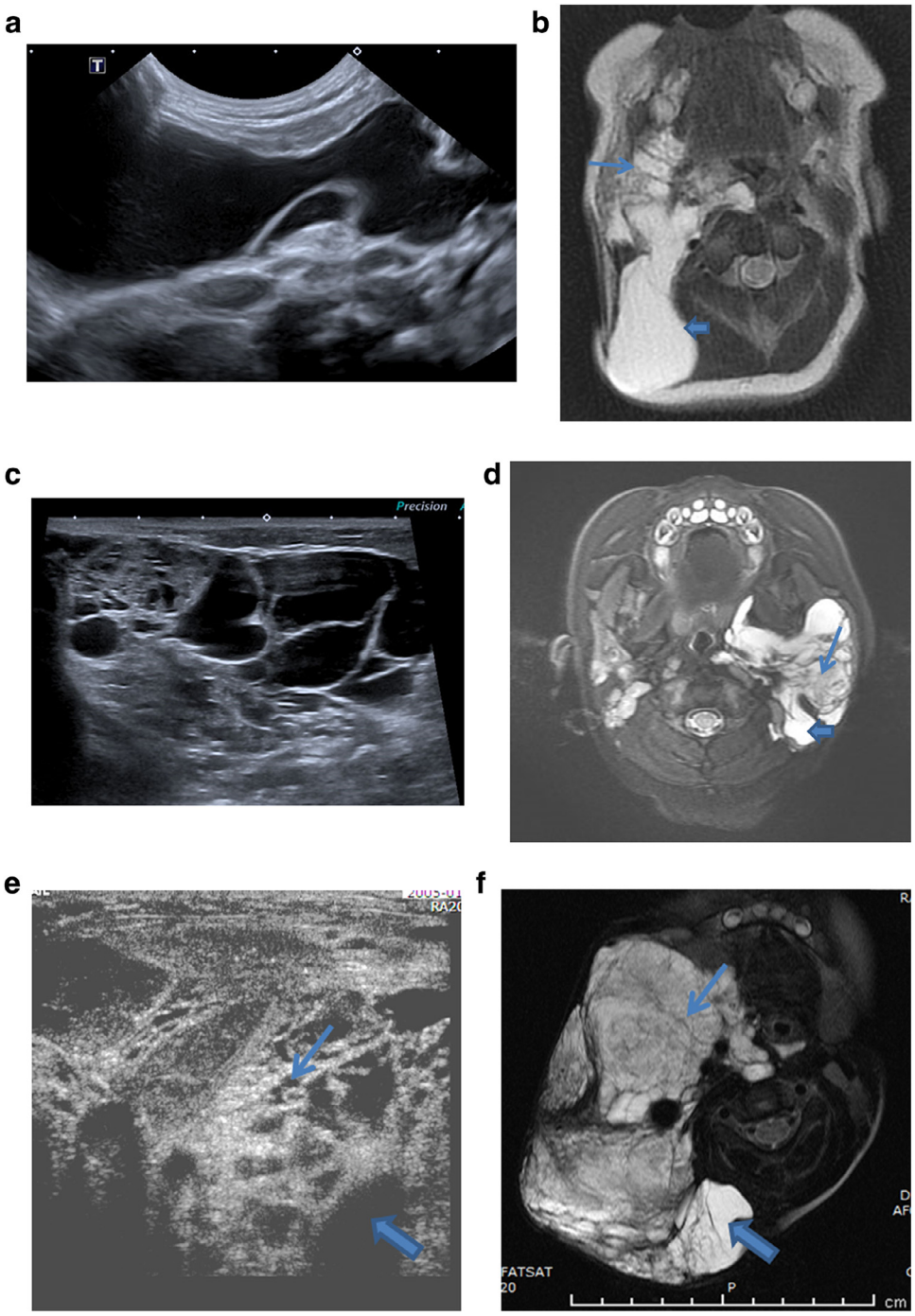

Figure 2 (a, b) Type 2a mixed LM: cysts <1 cm: 10% (arrow); cysts >1 cm: 90% (arrowhead). (c, d) Type 2b mixed LM: cysts <1 cm: 50% (arrow); cysts >1 cm: 50% (arrowhead). (e, f) Type 2c mixed LM: cysts <1 cm: 80% (arrow); cysts >1 cm: 20% (arrowhead).

echogenicity. On color Doppler interrogation, absence of flow is observed in LMs except for the septa where high resistive arterial or venous flow can be detected. Pure microcystic LMs appear as ill-defined and hyperechoic and have a solid appearance due to the numerous interfaces of the microcystic walls.[19,20] Mixed cystic LMs consist of cystic and solid components, related to the size of cysts.[21] Contrary to venous malformation (VM), the lesion is partially or not compressible.

MRI shows a well-defined border, lobulated, septated mass with low-signal intensity on T1 and high-signal intensity on T2. Because of varying amounts of protein or hemorrhage within the lesion, LMs occasionally present with variable signal intensity on T1 and T2 sequences. Sometimes, the signal intensity of the content tends to be hyperintense to muscle on T1-W due to the protein nature or hemorrhagic cyst. No gadolinium enhancement is seen except for the septa. However, superimposed inflammation can lead to significant enhancement of the septa and peripheral enhancement.[19] The percentage of cysts ≥ or < to 1 cm is estimated in the total volume of the lesion to define the type of LM. Pure

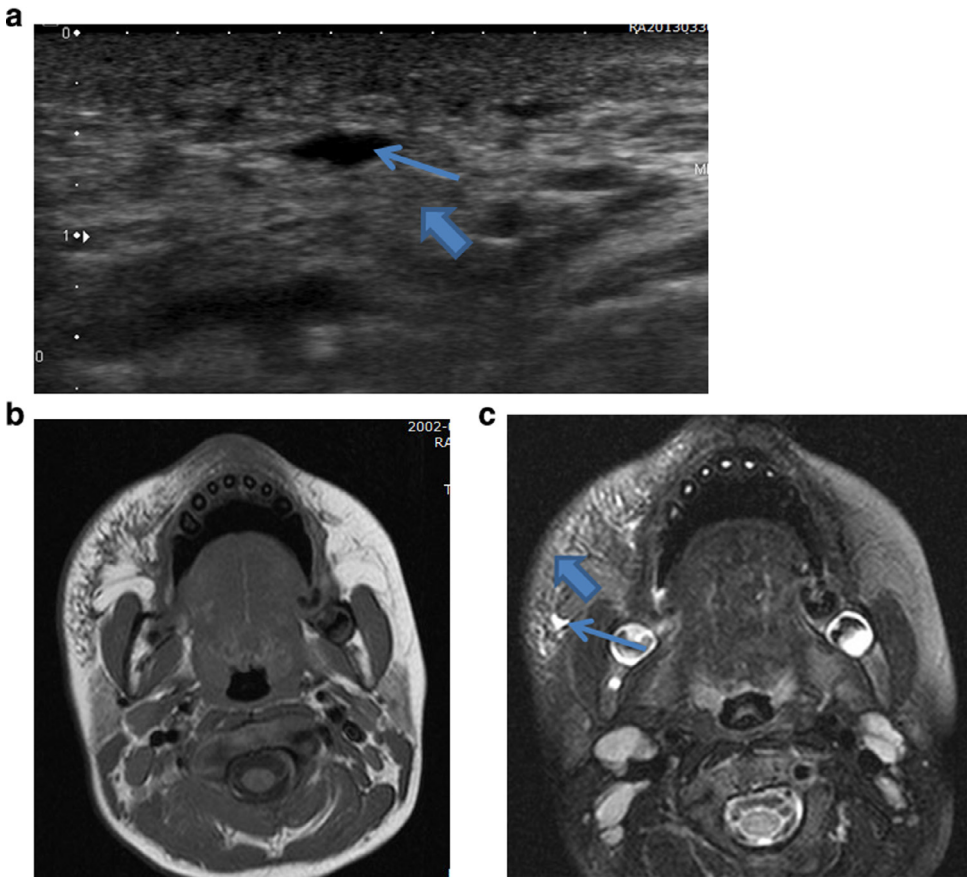

Figure 3 (a-c) Type 3 microcystic LM: cysts <1 cm (arrow) with solid matrix (arrowhead).

microcystic LM is an ill-defined lesion, isointense on T1 and displays a heterogeneous signal on T2, with or without a slight heterogeneous enhancement on T1 postgadolinium. Stranding of the adjacent subcutaneous fat may be present.[21]

Indications for Treatment

Cervicofacial Lesions

Cosmetic concern is the primary indication for treatment. It is important to clarify the expectation prior to proceeding with treatment. The complete surgical resection of LMs at any price should be avoided if there is potential risk for functional damage. Moreover, recurrence is often observed after surgery. Involvement of aerodigestive tract and orbit needs a special attention to avoid respiratory compromise or loss of vision. Feeding, speech disorders, and dysgnathia are also challenging problems.

Unilateral macrocystic or mixed LMs rarely create an airway compromise which necessitates an intubation or immediate treatment. We should not be influenced by the size of the lesion on imaging and rely on patient symptoms.

Even though the macrocystic or mixed lesion infiltrates the pharyngeal space and creates a compression effect on the airway, most of the time the child has no repercussion on the clinical parameters. Bilateral LMs of any types with an infiltration of the buccal floor and tongue are more problematic and deserve a special attention, particularly when the patient has a microcystic LM involving the airway with an infiltration of the laryngeal, bronchial, circumferential subglottic, and tongue. De Serres et al's staging of the head and neck LMs is helpful in determining treatment.[5] They reported that the complication rate of surgery and the number of therapeutic interventions correlated to a more advanced stage.[7] For the tongue and oropharyngeal area, the Cologne Disease Score is useful in determining the risk and feasibility of surgery.[6,22] Only stages I and IIa can be completely resected. In stages IIb, III, and IV, the complete resection should be avoided to preserve organ function.

LMs involving the thorax, axillary, mediastinum, and/or extremity regions can be treated for esthetic concern, bleeding, or lymphatic fluid leak or pain. However, in case of asymptomatic LMs of the mediastinum, the treatment is controversial as observation, surgery, or sclerosing treatment can be proposed. In our group, most of them were treated by sclerosing treatment after discussion with the family and the multidisciplinary team.

Treatment

Observation

The vast majority of LMs do not need immediate treatment. The timing of treatment is decided with the parents and the multidisciplinary team. In untreated patients, spontaneous regression was reported in 12.5%[23] and in 50% of observed patients, with a follow-up of 33.4 months.[24] Kennedy et al reported 11 of 12 untreated patients with a spontaneous

improvement of the LM, with 8 patients showing complete resolution.[25] In our experience, most of the patients having spontaneous regressions of the LM came back to the clinic after more than 1 year with a recurrence of their LM. The majority had a history of bleeding in the LM.

Surgery

Surgery was the first treatment for the management of LMs before the introduction of sclerotherapy. A systematic review of the treatment of head and neck LMs was done with the conclusion that LM treatment can be done effectively with surgery or sclerotherapy but the standardization of LM description before and after treatment is missing in most publications, making impossible the comparison of treatment outcome.[26] However, large series of LMs treated with surgery had a significantly higher failure rate or recurrence rate, especially for the head and neck LMs. Complications are observed in 35% with facial nerve injury (5.9%-33%), bleeding (1.6%), seroma (9.8%), and infection (2.5%-5.9%). The rate of clinically significant recurrence has been reported as high as 17% following complete excision and 40% following incomplete excision.[27,28] In our experience, we opted for surgical resection in cases with residual skin, or in cases involving symptomatic or esthetic concerns after fair or poor response to sclerotherapy treatment. Following sclerotherapy, LMs will never completely disappear on MR imaging, but there is no need for further treatments in asymptomatic patients.

Sclerotherapy

Techniques

There is no consensus for the administration of steroid or antibiotic before LM sclerotherapy. In our institution, we do not routinely give antibiotic before sclerotherapy. Only patients with LMs affecting the tongue or buccal floor are given a combination of IV Cefazolin (25 mg/kg/dose for a maximum dose of 2000 mg) and Dexamethasone (0.5/mg/dose, for a maximum dose of 20 mg) just before the procedure.

Sclerotherapy treatment can be performed under IV sedation with ketamine (10 mg/1 mL): 0.8 mg/kg for a maximum dose of 40 mg and Versed (1 mg/1 mL): 0.08 mg/kg for a maximum dose of 4 mg. However, most of our patients were treated under general anesthesia, mainly because of their young age and the location of the lesion.

A puncture of the cyst using a 20-24 G angiocath needle is performed under continuous ultrasound guidance. We aspirate the fluid as much as we can and then we inject a small amount of contrast medium under fluoroscopy to confirm the intralesional position of the angiocath needle. The volume of the sclerosing agent to be injected is approximately the volume of aspirated liquid. Acord et al proposed to manually make additional side-holes in a sheathed needle to allow better fluid aspiration in small cavities.[29] The sclerosing agent is usually injected under fluoroscopic guidance. However, if ultrasound allows to properly visualizing the LM, we perform the sclerosing agent injection using this modality. We can observe the distribution of the sclerosing agent through the different cysts. Under ultrasound, when a portion of the cyst seems to be outside of the area that is injected, we perform another puncture. In our institution, we do not remove the sclerosing agent after the injection. Even if the LM has an important volume, we never inject more than the maximum of recommended dose of sclerosing agent. In our experience, it is surprising to notice how effective can be sclerosing agent with only 1 or 2 punctures.

When Do I Decide to Drain?

In our institution, we rarely use a drain. Our criterion for using a drain is not related to the size but to the location of the LM. We tend to use drains when the LM is around the tracheal area or in LMs who have not responded after a first sclerotherapy session. A compression effect on the trachea with a normal mucosa of the airway is rarely an indication for a drain or prolonged intubation. If we decide to install a drain, a 5 or 6 French pigtail catheter is placed under ultrasound guidance. We inject the sclerosing agent through the catheter, allow to dwell for 12 hours, then open the drain. We repeat the sclerosing treatment through the drain daily until there is no significant drainage (below 10% of the original output from the catheter). In most of our cases, the drain is removed after 48-72 hours. In the literature, some authors reported that sclerosant can be left to dwell between 4 hours[30,31] and 6 hours.[29] Acord et al connect the drain to bulb suction.[29]

For microcystic LMs with tiny cysts, we cannulate the cysts with a 25-27 G hypodermic needle under ultrasound guidance. However, considering their small size, aspiration of the lymphatic fluid is usually not possible. In these cases, we inject slowly under US and/or fluoroscopy to observe the distribution of the sclerosing agent. Doxycycline foam can be used, mixing 5 cc of doxycycline with 2 cc of air through a 3-way stopcock to improve the penetration of the tiny cysts. Acord et al reported doxycycline foam with albumin.[29]

Acord et al routinely use low-dose C-arm CT to ensure that treatment covers the entire lesion. In my experience, to avoid radiation even if it is a low-dose CT, we do not use it in our pediatric population. According to our experience, we have many times used sclerosing agents with only 1 puncture and observed an excellent response to treatment. We are not convinced that C-arm CT acquisition is necessary to evaluate the spreading of the sclerosing agent in all cystic components. The inflammatory reaction produced by the agent in the lesion is sometimes enough to get a good response.

For pharyngeal and/or laryngeal involvement with mixed or microcystic LMs, we proceed with an open mouth system with the assistance of the ENT to get a direct access to the lesion through the mucosa and use the procedure described above.

Another interesting technique is reported by DaRos et al: a lymphographic-like technique for the treatment of microcystic LMs.[32] The procedure is performed under fluoroscopic and sonographic guidance using a 22 G needle. For tiny cysts (<3 mm), they did not wait for lymphatic fluid reflux in the needle. Four-to-eight needles were inserted into the microcystic component of the LM in each treatment session, depending on the volume of mixture available based on the

patient's weight. Each needle was connected to a pump with a line comprising a dead space of about 1.8 mL. Bleomycin was diluted as follows: 15 mg of Bleomycin in 5 mL of saline and 3 mL of contrast to obtain 8 mL of mixture. This total volume of 8 mL was injected at each session in adults. Because a dose of 0.5 mg/kg per session was injected in children weighing <35 kg, the volume of mixture was determined as follows: 8 mL of mixture every 30 kg of weight. Each line was then filled with 1 mL of mixture, and the remaining line dead space was filled with saline. In low-weight babies, when the total volume of mixture was <4 mL, contrast medium diluted with saline (50%-50%) was added to obtain a volume of 4 mL to fill 4 syringes. A 10-cm long gas bubble between Bleomycin mixture and saline was used to avoid mixing both solutions. Finally, the line was connected to a 10-mL electronic syringe pump filled with 1 mL of saline, and the infusion was administered at a flow rate of 0.7 mL/h. At the end of the injection, a low-dose CT scan was obtained to check diffusion of the mixture in the LM.[32]

Post-Treatment

Most of patients treated for LMs are discharged after 8 hours, except for infants younger than 6 months and patients with stages IV, V head and neck LMs and patients with LMs of the tongue. In our experience, most of our patients have no significant pain after the procedure. If they need analgesia, we prescribe acetaminophen and Ibuprofen. Phone follow-up is performed 24-48 hours after the procedure and the patient is scheduled for clinical follow-up 3 months after treatment. We do not systematically monitor for hypoglycemia and metabolic acidosis. We never exceed the dose of 20 mg/kg of doxycycline, max 1000 mg per session. Cahill et al recommend a routine monitoring for neonates who receive large doses of doxycycline (>150 mg).[33]

Sclerosing Agents

Sclerosing agents used for LMs have less significant side effects than when used for venous or arteriovenous malformations. However, nerve injury, skin necrosis, blistering are reported with all sclerosing agents but are more frequent with ethanol and sodium tetradecyl sulfate (STS). Hemoglobinuria from hemolysis with STS leading to renal impairment is usually resolved with hydration and is described in VM.

Doxycycline (Figs. 4-8)

Doxycycline is an antibiotic of the tetracycline group. It was first reported in the treatment of LMs by Molitch et al.[34] Doxycycline has antitumoral properties, is an inhibitor of matrix metalloproteinase, as well as suppresses vascular endothelial growth factors[35] during angiogenesis or lymphangiogenesis which may exert a therapeutic effect. Doxycycline powder (vials of 100 mg) is mixed with 5 cc of saline (0.9%) and 5 cc of contrast medium (Omnipaque 180) for a final concentration of 10 mg/mL. Doxycycline foam is a mixture of doxycycline with albumin or aerated saline through a 3-way stopcock with 30 agitations and has been recommended for microcystic LMs.[29] The dose is 20 mg/kg with a maximum dose per session of 1000 mg of doxycycline. In our experience, the incidence of side effects is very low, mainly pain. Skin discoloration over the site of the LM is sometimes seen in our experience but is rarely reported in the literature. Side effects reported in the literature were pain, swelling, recurrent infection.[30] Anecdotic cases of hypoglycemia, metabolic acidosis were also reported but with a higher dose than 20 mg/kg.[33]

OK-432

OK-432 (Picibanil, Chugai Pharmaceuticals, Tokyo, Japan) is a lyophilized powder of low-virulence Su strain of streptococcus pyogenes of human origin (group A, type 3, Su strain) incubated with penicillin G. It induces apoptosis of lymphatic endothelium/local cellular inflammatory reaction. It is available in 0.1 mg of OK-432 powder that is dissolved in 10 cc of serum saline (0.9%). The maximum dose per session is 0.3 mg.[36] The side effects are fever, inflammation, pain, and swelling. OK-432 is contraindicated with patients allergic to penicillin.

In our institution, OK-432 is not authorized by the ethic committee due to the potential risk of Creutzfeldt-Jakob disease. As far as I know, this was however never reported.

Bleomycin

Bleomycin is an antitumoral antibiotic produced by a strain of *Streptomyces verticillus*. The standard Bleomycin is a mixture of A2 and B2 and 10 to 15% of A5. In Pingyangmycin (used in Asia), the greatest proportion consists of Bleomycin A5. The pharmacologic profile and the molecular structure are similar but the terminal amine moiety is not. Bleomycin inhibits DNA synthesis, destroys the endothelial junction, and promotes endothelial cells transforming into fibroblast. Bleomycin is metabolized by Bleomycin hydrolase. Bleomycin is well distributed with high concentration in skin, lung, peritoneum, and lymphatics due to the low level of Bleomycin hydrolase, an enzyme for detoxifying Bleomycin. Forty-five percent is absorbed systemically after intrapleural injection. It is excreted in the kidney and inactivated in liver and intestinal wall. Histologic changes of resected tissues after sclerosing treatment with Bleomycin A5 showed that the lymphatic endothelial cells were destroyed, and lymphatic vessels were obstructed.[37]

The Bleomycin dose is 0.5 mg/kg for a maximum of 15 mg per treatment session. One unit equals 1 mg of Bleomycin. This drug is mixed and delivered by our oncology pharmacy. Bleomycin is delivered at 2 mg/mL in NaCl 0.9% in 10 mL syringes (maximum volume of 5 mL per syringe). The dose is rediluted at 1 mg/mL of Bleomycin with an equal volume of contrast material in the angio room. A specific chart must be completed with the doses administered and the cumulative doses before the day of the procedure. For oral lesions, 1 dose of IV Cefazolin (25 mg/kg/dose, max 2000 mg) is administered 30-60 minutes before Bleomycin injection. If the patient is allergic to penicillin or to cephalosporins, IV

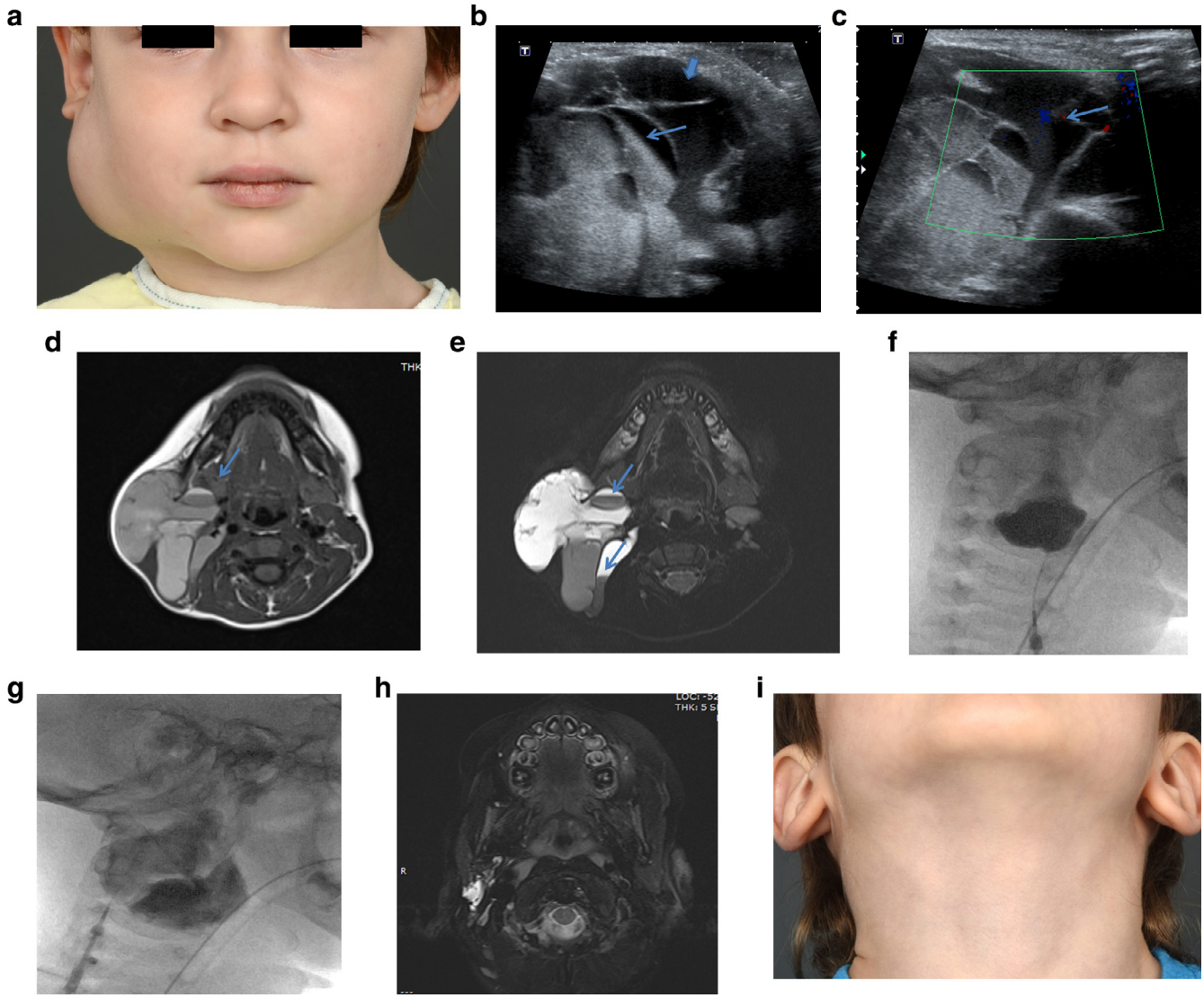

Figure 4 (a) Three-year-old boy with sudden apparition of a cervical lesion. (b) US demonstrated a multicystic lesion. Some cysts were hyperechoic with fluid-fluid levels due to hemorrhage (arrow) and others were anechoic (arrowhead). (c) Color Doppler revealed vessels in the septa (arrow). (d) Axial T1-W image showed a well-defined multiseptated mass in the parapharyngeal space behind the submandibular gland (arrow), hyperintense compare to the muscle due to the presence of hemorrhage. (e) Axial T2-W FS showed the multicystic lesions with hyperintense content and fluid-fluid levels (arrows). (f, g) Sclerotherapy was performed under general anesthesia. Two punctures were performed under US and fluroscopy. Fluoroscopy capture showed (i) first puncture with injection of 6 cc (60 mg) of doxycycline and (ii) second puncture with 7 cc (70 mg) of doxycycline. (h) Two years after sclerosing treatment, MRI showed a small residual behind the parotid gland. (i) The patient had no visible lesion in his neck.

clindamycin (15 mg/kg/dose, max 600 mg) is given. If there is risk of compression/edema of the respiratory tract, we give Dexamethasone (0.5 mg/kg/dose, max 20 mg) IV for 1 dose. The pediatric dose is not well documented. We estimate an equivalence of 200 U/m^2.

Side Effects

Skin lesion and pulmonary dysfunction were well described as side effects of Bleomycin in the oncologic literature. Even if pulmonary fibrosis is said to have no direct relation with LM sclerotherapy, greater reliance must be placed in the oncology literature.

The common mucocutaneous lesions described as side effects of Bleomycin therapy are pigmentation (~50%), alopecia (~50%), and flagellate dermatitis (8%-66%).[38] The incidence of flagellate dermatitis and subsequent hyperpigmentation in the skin induced by Bleomycin has been reported between 8% and 22%.[39] The onset of the lesion can appear at day 1 and up to 9 weeks after the administration by any route: IV, intramuscular and topical.[40] In our patients treated with Bleomycin, we had 2 cases of flagellate dermatitis with a low dose of Bleomycin of 10 U.

The effects of Bleomycin can be harmful and fatal. With total cumulative doses of 400 units, the development of pulmonary fibrosis is seen in 10% of adult patients without other risk factors and death rate is 1%-2% among these patients.[41] Below this threshold, the incidence of pulmonary toxicity is estimated to be

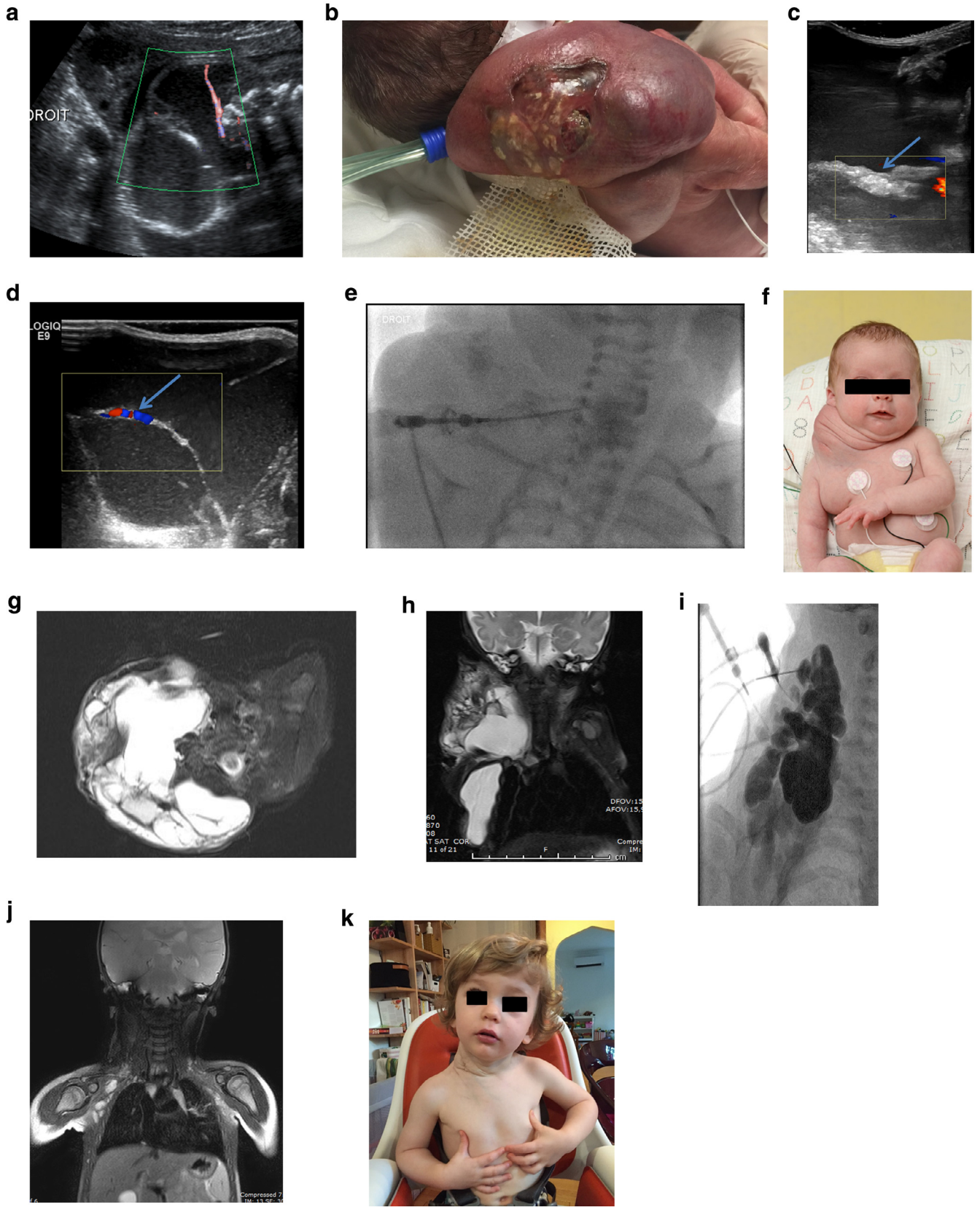

Figure 5 (a) Fetal US at 16 weeks revealed a head and neck multilocular cystic mass. (b) Baby was born at 1.9 kg with a bluish cevicothoracic mass with ulceration and cutaneous bleeding which was closed with suture by the plastic surgeon. (c) At born, US showed a multilocular cystic lesion with debris (arrow) inside the cystic cavities due to hemorrhage. (d) Color US demonstrated vessels in the septa (arrow). (e) First sclerotherapy was performed at 2 months. At that time, the premature baby was growing well with no respiratory distress or feeding problem. One puncture with

between 3% and 5%.[42] Pulmonary dysfunction was reported with a median dose of 120 mg/m^2[43] and 60 U/m^2.[44] De Aliva et al[45] reported pulmonary function test abnormalities like hyperinflation, obstructive lung disease, restrictive lung disease, and nonuniform distribution of ventilation in asymptomatic patients treated with Bleomycin. Four main types of pulmonary toxicity are seen: subacute progressive pulmonary fibrosis, hypersensitivity pneumonitis, organizing pneumonia, and acute chest pain syndrome. The pediatric dose is not well documented. We estimate an equivalence of 200 U/m^2. The exacerbation of Bleomycin to induce lung injury was seen with radiation, other chemotherapeutics agents like cyclophosphamide, vincristine, doxorubicin and methotrexate, and renal insufficiency. The risk of Bleomycin toxicity is magnified by a high dose of inspired oxygen.[41] Oxygen may exacerbate pulmonary toxicity several years after treatment with Bleomycin.[46,47] Careful monitoring of fractional-inspired oxygen must be at the lowest tolerated oxygen concentration (89%-92%) for any surgical or interventional procedure requiring oxygen support. The onset of clinical manifestations usually occurs subacutely between 1 and 6 months after Bleomycin treatment but may occur after 6 months. The classic pattern on CT scan is basal subpleural opacities or fine nodular densities followed by a honeycombing and fibrosis.

If you use Bleomycin as a sclerosing agent, some precautions should be taken. The manipulation of the product and disposal of the material in a specific container must be established. In the angio room, staff and patients must wear eyes protection and a special mask. The Bleomycin is incompatible with D5%. The anesthetist must keep the oxygen level at 89%-92%. We have no specific protocol for monitoring the pulmonary function test.

Absolute Ethanol

Absolute ethanol denatures cellular protein and destroys the endothelium of the vascular walls. Even if the literature reports a maximum dose of 1 cc/kg, we recommend a maximum dose of 0.5 cc/kg per session to avoid side effects. Side effects reported are respiratory depression, cardiac arrhythmias, seizures, rhabdomyolysis, and hypoglycemia.[48] Complications were often observed, reaching up to 61% of the treated patients with a mean weighted percentage of 18%.[49] However, the side effects were reported especially for embolization of AVM with ethanol.

STS

Sotradecol is a detergent that disrupts the normal architecture of the lipid bilayer of the cell membrane of the endothelial cells, leading to increase membrane permeability and allowing for greater membrane penetration for intracellular protein denaturation and cell deaths.[50,51] STS is used in liquid form or as foam. STS comes in vials of 2 cc of 1% (10 mg/mL) and 3% (30 mg/mL). The maximum dose of STS is 10 cc.

STS foam is a mixture of 1 cc of STS with 1 cc of ethiodized oil (Ethiodol; Savage Laboratories, Melville, NY) to 3 cc of air/albumin mixed with a compatible 3-way stopcock. The combination of agents is done for improving the penetration and the contact of the sclerosant through the LM.

Hill reported the use of STS injection followed by immediate aspiration, then followed by ethanol injection and aspiration for patients with orbital LMs. The author reported that STS effectively releases transmembrane lipoprotein from the LM cell membranes, leads to increase membrane permeability and allows for greater membrane penetration of ethanol for intracellular protein denaturation and cell deaths.[51]

Polidocanol

Polidocanol is a hydroxypolyether that is nonaethylene glycol. It is a detergent which creates the destruction of the endothelium. It is used in liquid or foam form. The complications reported are similar to STS.

Medical Treatment

Sirolimus

Sirolimus is an mTOR inhibitor and has been shown to inhibit angiogenesis by blocking the AKT/PIK3 pathway and reducing the production of VEGF and responsiveness of its receptors.[52,53] Adams et al reported 50% of microcystic LM regression in a series of 5 patients.[54] Dexamethasone inhibits the production of VEGF-A, IL-6, and matrix metalloproteinase-1. Greenberger et al reported a synergic effect with the combination of Sirolimus and steroid as an antiangiogenic effect.[55]

The clinical side effects of Sirolimus are mucositis, stomatitis, infections, headaches, hypertension, hypercholesterolemia, increased liver enzymes, defect healing, renal dysfunction, thrombocytopenia, leucopenia, anemia, microcytosis, and rarely interstitial pneumonitis. Due to the potential risk of immunosuppression with Sirolimus, a systemic prophylaxis of pneumocystis with co-trimoxazole or pentamidine has been suggested.[56]

In our experience, we reserved Sirolimus for complex or refractory LMs with functional problem in association with sclerosing treatment. We think that the association of Sirolimus with sclerosing treatment has a synergic effect and it is useful to decrease the length of time of medication and the recurrence.

injection of 40 mg of doxycycline (maximum dose) was performed. (f) clinical photo (g) axial T2-W FS, and (h) coronal T2-FS showed the multiloculated lesions with less than 20% of cyst <1 cm. (i) At 13 months, we repeated the sclerosing treatment with 4 punctures and a total of 100 mg of doxycycline was injected. At 6 weeks, (j) Coronal MR at 19 months showed a significant regression of the LM with residual cyst. (k) Clinical photo at 2 years old.

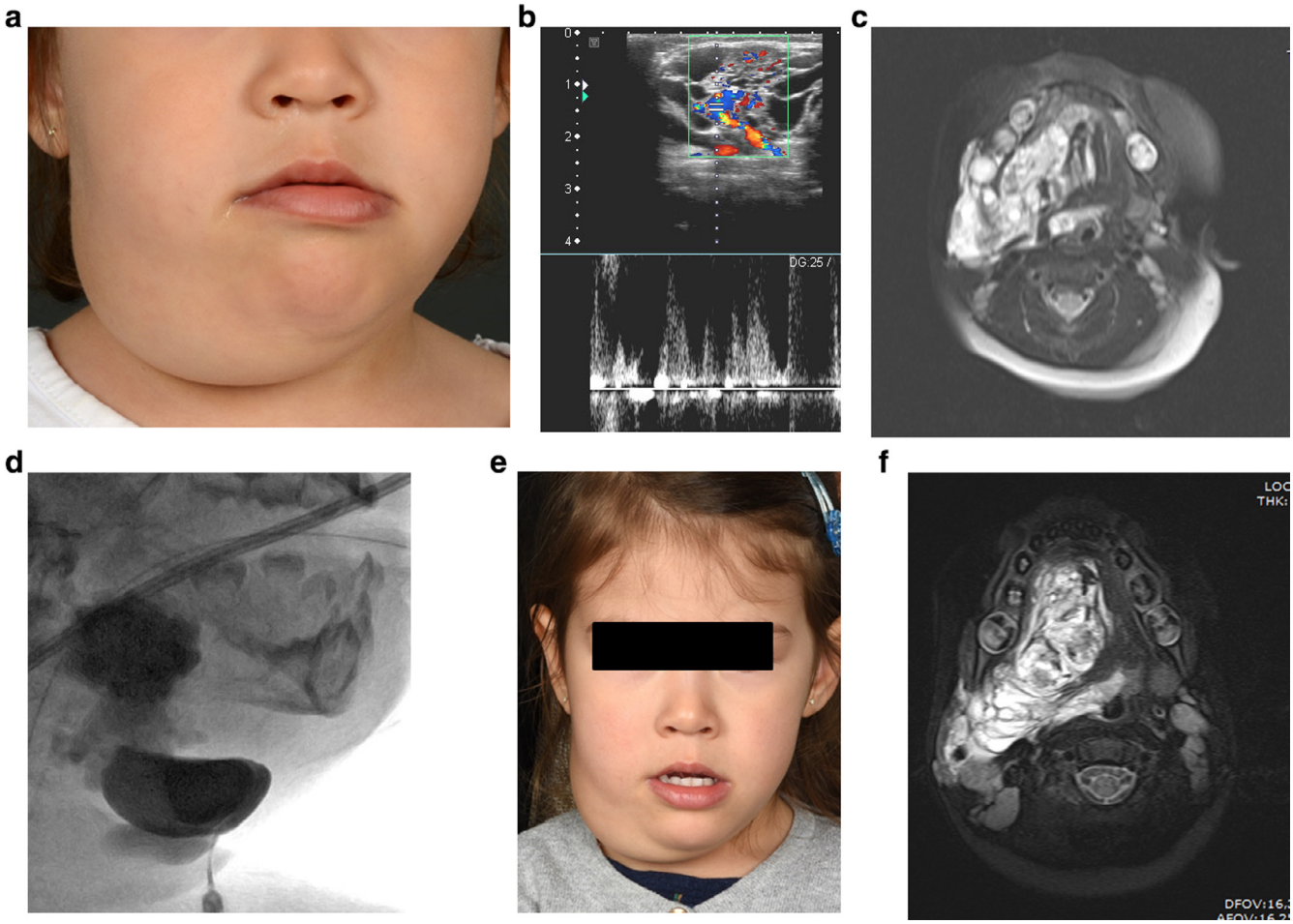

Figure 6 (a) One-year-old girl born with a right head and neck lesion. (b) Color Doppler US revealed a multicystic lesion with macro- and microcysts with vessels in the septa. (c) Axial T2-W FS MR showed a well-defined type 2c LM in the parotid gland, buccal floor and right parapharyngeal space. (d) She had 2 sessions of sclerotherapy under US and fluoroscopy control, respectively with 100 mg of doxycycline at 12 months and 100 mg of doxycycline at 17 months. (e) Fourteen months after the last sclerosing treatment, the clinical photo revealed a partial response despite the (f) axial MR T2-W FS which showed no improvement.

Topical Sirolimus

The minimum effective concentration of topical Sirolimus recommended is 0.4%, applied at least once a day.[57] Topical Sirolimus 0.1% solution is efficient and well tolerated in children with cutaneous manifestations of extraluncular LMs.[58]

Sildenafil

Sildenafil is a selective inhibitor of phosphodiesterase-5 (PDE-5). Therapeutic response in 6 out of 7 patients without significant side effects was reported.[59] However, some reports have shown that Sildenafil had no effect and recommended caution before prescribing Sildenafil empirically for LMs.[60-62]

Alternative Treatment Options

Laser

Laser therapy, CO_2 alone or in combination with the Nd:Yag laser, was used for the treatment of microcystic hemorrhagic parts of LMs with skin angiokeratosis or in microcystic LMs of the tongue or superficial dermal lesion.[63,64] This treatment is rarely curative but may improve symptoms.[60]

Outcome of Sclerosing Treatments

No conclusion can be reached about the superiority of sclerotherapy or surgery treatment related to the heterogeneity of procedure and outcome reporting. However, some authors reported that stages I-III head and neck LM lesions represented more than 80% of all head and neck LMs and had a similar response to surgery and sclerotherapy.[65] Stages I and II LMs do not cause functional compromise, that is, airway obstruction, dysphagia, and have been reported to shrink without invasive therapy in up to 30% of cases.[9,66] Higher stages IV and V LMs, causing functional compromise, are bilateral, are usually predominantly microcystic, possibly associated with lymphopenia and tertiary lymphoid organ formation, and are prone to persist and be recalcitrant to standard therapies.[9,67,68]

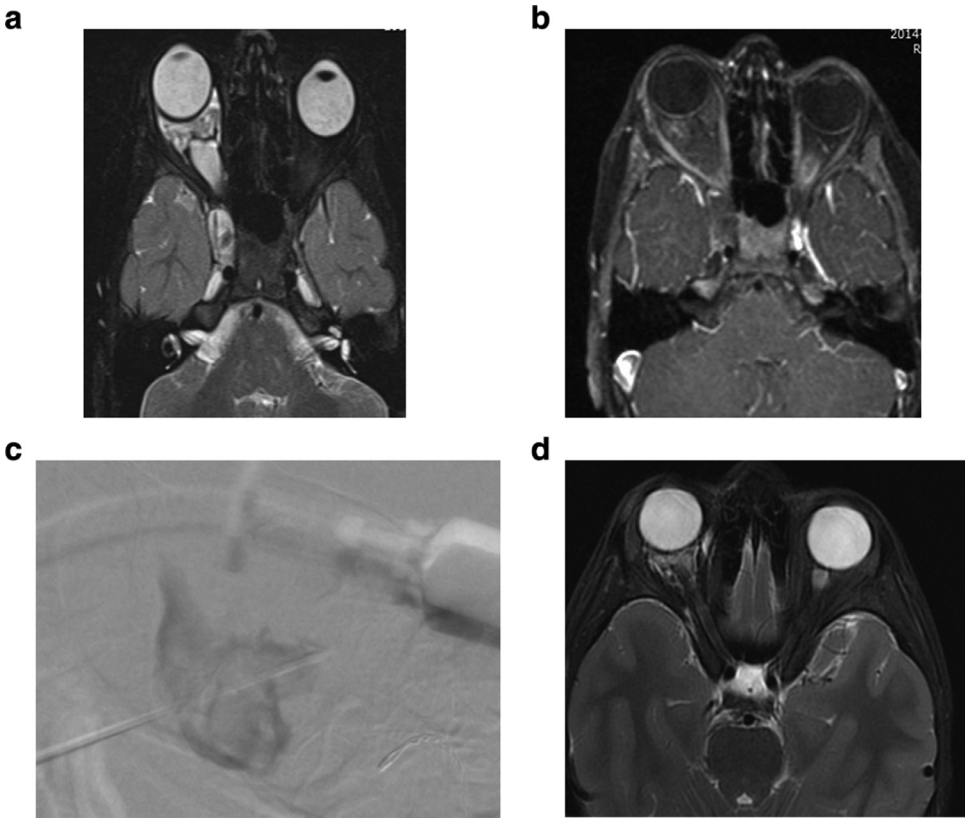

Figure 7 Four-year-old boy consulted for a sudden proptosis of his right eye. (a) Axial T2-W FS MR showed multicystic retro-ocular hyperintense lesion on T2-W FS and (b) no enhancement of the lesion after gadolinium injection. (c) Under US, percutaneous puncture of the cyst was performed after mobilization of the eye by the ophthalmologist. Opacification of the cyst under DSA acquisition: 1 cc (10 mg) of doxycycline was injected. Same technique was performed 8 months after first session. One cc (10 mg) of doxycycline was injected. (d) Follow-up 3 years post-treatment, residual cysts were still present. The patient was asymptomatic.

A meta-analysis found that surgical recurrence rates are around 30%, whereas the morbidity is between 2% and 6%.[23,69]

Acevedo[4] reviewed 1876 articles and retained only 22 articles concerning nonsurgical therapy in LMs with more than 5 patients. In most of the articles, OK-432 and Bleomycin were used. Respectively, complete or excellent response was estimated at 23.5%-35.2%; good response at 16.9%-37.1%; fair response at 15.4%-18.4%; and no response was observed in 0%-11.6%. Seven major complications were found including 2 deaths: 1 from pulmonary complication after 3 months of treatment with Bleomycin[70] and 1 died from pneumonitis after Bleomycin treatment.[71] These events are not clearly related to Bleomycin. Orbital decompression (n = 1), emergency intubation (n = 2), tracheostomy (n = 1), and transient facial nerve palsy (n = 1) were reported after OK-432 sclerosing treatment.[71-73]

Smith et al, in a series of 117 patients treated with OK-432, reported 68% of complete or substantial response with 94% of macrocystic LMs, with a recurrence rate of 9%.[74] Spontaneous resolution was seen in less than 2%. The authors compared their series with OK-432 with surgical outcome data from 4 series and found that OK-432 was 4 times more likely to be successful than surgery and was associated with one-tenth the number of adverse complications ($P < 0.001$) contrary to Balakrishnan et al who reported no significant difference in efficacy between surgery and sclerosing treatment in 174 patients.[65]

A meta-analysis was done on intralesional Bleomycin for vascular malformation by Horbach et al with an overall good/excellent size reduction in 84%.[49] Complications observed in LM treatment were facial nerve palsy (n = 1), hyperpigmentation in 0.8%, transient swelling and pain.

A systematic review on doxycycline for the treatment of head and neck LMs was reported by Chen et al.[75] Five studies were included with 84.2% of >50% of response, and only 1 session was performed in 60.5%. No microcystic LM was included. The doxycycline was well tolerated with minimal side effects like pain.

Cahill et al[33] reported a series of 17 children, 10 macrocystic LMs and 7 microcystic LMs with a total of 49 procedures using doxycycline, ethanol, and STS. Improvement on imaging was observed in 76% (11/17). Seven complications were reported: 28 out of 49 procedures required a postprocedure prolonged intubation with a duration of 8 days at ICU (2-28 days).

Regarding microcystic LMs, Wu et al[75] reported excellent 33.33% and good 42.86% response with Bleomycin A5 with

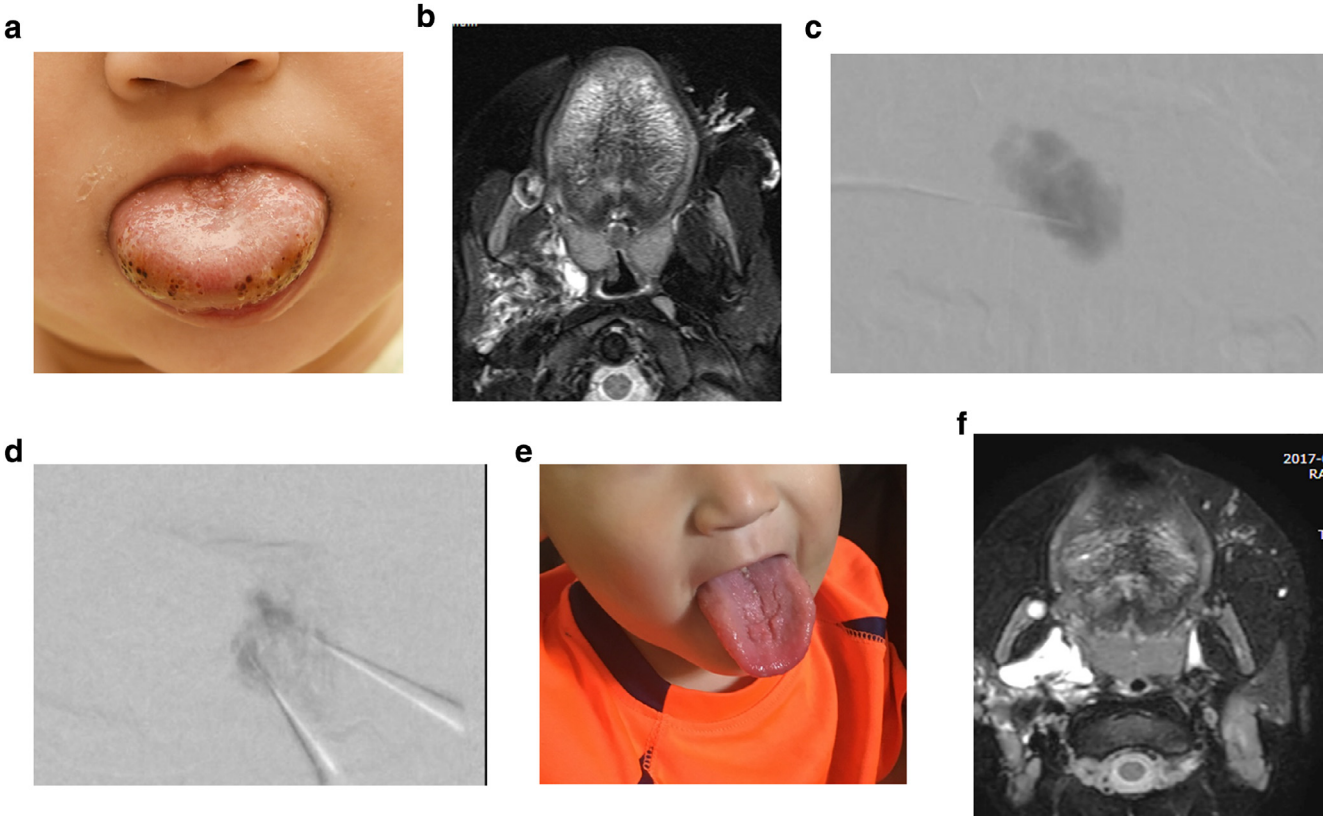

Figure 8 (a) Twenty-one-month-old boy with head and neck LM with tongue involvement. After discussion with the parents, we decided to treat the tongue. (b) Axial T2-W FS showed microcystic LM of the tongue. (c, d) Under GA, we performed 3 punctures of the tongue with a 25 G needle with opacification of the tiny cyst. We injected 1.7 U of Bleomycin. After 4 months, we repeated the same procedure with 1.5 U of Bleomycin. (e) Clinical photo 1 year post-treatment, with a good resolution of the LM. (f) Axial T2-W FS control MR showed a good regression of the microcystic LM, after 2 sclerosing treatments with Bleomycin.

no major side effects. Chaudry et al[76] reported 38% of complete reduction and 58% of partial reduction and no response in 1 patient with Bleomycin intralesional injection.

Sirolimus has been used for severe lymphatic conditions with varied success.[3,54] A study of 19 patients with refractory cervicofacial LMs treated with Sirolimus from November 2012 to October 2016 at Boston Children's Hospital reported that 7 patients remained on uninterrupted Sirolimus therapy. Of the 12 who stopped therapy, 7 needed to resume Sirolimus due to symptom recurrence. However, all patients with cutaneous vesicles (n = 14) either had resolution or improvement while on Sirolimus.[77]

Impact of LM Classification on Management

The classification of Malic et al[18] subdivides the microcystic LMs in LMs with communication and LMs without communication. There is no explanation on the role of connections between the lymphatic channels which are observed in complex LMs and not in simple LMs. On the other hand, we have known for many years that most of the cysts in LMs communicate between each other as demonstrated by injection of contrast under fluoroscopy. Probably some of them had no or minimal communication.

Malic et al[18] reported that open-cell microcystic lesions respond better to OK-432 than closed-cell microcystic lesions and lymphatic channels. This is probably related to a better diffusion of the sclerosing agent. Many articles on the efficacy of Bleomycin sclerotherapy were reported by Asian teams who do not use fluoroscopic guidance for sclerotherapy and sometimes no ultrasound guidance either, most of them injecting through a needle after aspiration of cyst fluid under visual control. Thus, diffusion of Bleomycin in the interstitial tissue followed by resorption with the lymphatic system could explain the good efficacy of this approach even if the cysts are not targeted specifically.

In our experience, following sclerotherapy, LMs will never completely disappear on MR imaging, but there is no need for further treatments in asymptomatic patients. The justification of radical surgery, which carries a high complication rate in a benign lesion, needs to be discussed with caution.

Conclusion

Simple (cystic) LMs are not a result of disrupted vasculogenesis but arise from genetic abnormalities in specific cells within the malformation. Systematic review of existing literature to determine the respective outcome following surgical resection, sclerotherapy and laser therapy is difficult due to differences in patient evaluation before and after treatment

and poor definition of endpoints. Doxycycline is the first choice for sclerotherapy treatment not only for its efficacy but for also for its safety. OK-432 is a good option if the product is available and authorized in your hospital and country. Bleomycin must be reserved for LM cases refractory to doxycycline or OK-432, particularly for microcystic LMs. Laser and surgery are other therapeutic options, adjuvant to sclerosing treatment.

Targeting specific cellular receptor in patients with LMs with specific molecular with new drugs or local treatment will probably improve the management and outcome of LMs. However the dose, the length of treatment, the toxicity, and the long-term complications are important to discuss with the patient and the family. A multidisciplinary team is essential to offer the best management and therapeutic options to the patients with LMs.

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