Cervical Lymphangiomas in Children: Non-Surgical Treatment with Focus on Sclerotherapy. Literature Review

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Methods: A literature review of the last fifteen years about sclerotherapy of cervical lymphangiomas in children was performed and the main sclerosing agents were reported, highlighting the nature, the mechanism of action and the rates of success, recurrences and complications related to each and every substance; furthermore, the several steps of the procedure are illustrated. Alternative approaches are also mentioned.

Results: 47 articles were collected, mostly dealing with sclerotherapy with OK-432, bleomycin/pingyangmycin and doxycycline; other potential substances include, above all, sodium tetradecyl-sulphate and ethanol. Laser therapy and radio-frequency ablation are valid options in case of mucosal micro-cystic lesions; oral medications (e.g. Sirolimus) and the newest target-therapies are added to local treatments in some Series.

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Conclusions: Despite no univocal guidelines and the most recent "multi-approach" strategies, sclerotherapy represents the main non-surgical treatment for cervical lymphangiomas (especially when dealing with macro-cystic or mixed varieties) in children, and sometimes the first-line strategy. OK-432, bleomycin/pingyangmycin, doxycycline and sodium tetradecyl-sulphate represent the agents of choice, proving feasible with either micro-cystic lesions in several studies.

Advances in knowledge: Given the rarity of the disease, no large study fully reporting the results of sclerotherapy in the treatment of cervical lymphangiomas in children within the last years is available.

Keywords: cervical lymphangiomas, surgery, sclerotherapy, sclerosing agents.

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I. Background

Lymphangiomas (Lms) or, as recently preferred (according to ISSVA classification for vascular anomalies 2018), "lymphatic malformations" consist of lymphatic channels anastomosis and cystic spaces, as a result of abnormal connections between the lymphatic and venous systems or abnormal development or location of lymphatic vessels. Their incidence is 1/12000 births, accounting for 6% of all benign lesions of infancy and childhood. Cervico-facial lesions represent 75% of the cases and 80-90% become symptomatic within the first 2 years of life (both sexes equally affected) because of their progressive enlargement with growth. Many of them are congenital and often associated with other vascular or chromosomal abnormalities (e.g. Turner syndrome), without a clear familial tendency; however, they may arise or increase in size due to trauma, inflammation or lymphatic obstruction. Spontaneous regression within 18-24 months is documented in 1.6-16% of cases. Classification into macro-cystic, micro-cystic and mixed is based upon the diameter of the cysts. Presentation varies from asymptomatic, soft, not compressible, trans-illuminant neck tumefaction to dysphagia, malocclusion, sleep disordered breathing, respiratory distress and recurrent infections [1]. Since they are not encapsulated, they show infiltrative growth and often are not dissociable from airway, nerves and blood vessels [2].

Histology is similar to hamartomas, although some state a lymphangiectasic or neoplastic nature, without any malignant potentiality [3]. Ultrasonography documents mono- or multiloculate fluid-superfluid lesions with a substantial lack of flow with Doppler mode *(figure/patient 1-2).* Computer Tomography (CT) describes low attenuation masses with occasional fluid level and minimum septal and peripheral enhancement. Magnetic resonance imaging (MRI) detects iso- or hypo-signal on T1-weighted sequences and hyper-signal on T2-weighted sequences, a halo of enhancement around the septa of macro-cystic lesions and peri lesional lymphoedema *(figure/patient 2-3)* [4].

While small and asymptomatic lesions might benefit from purely conservative management (e.g.

compression, analgesia), larger and symptomatic (e.g. dysphagia, dyspnoea) malformations would require non-conservative treatment; this implies a multi-disciplinary approach (surgical, radiological, physician's) which varies according to each patient's characteristics and lesions, considering the lack of univocal indications for treatment as well as all those issues related to the young age of the patient (psychological or parental concern). Traditional surgical treatment has been considered for many years the gold standard for lymphatic malformations and is still considered the most definitive solution; however, as lymphangiomas are infiltrative, a complete eradication is often impossible [5]. This explains the relatively high percentage of recurrences (up to 27%) and intraoperative risks, with a mortality rate of 2-6%. At the present, surgery is indicated for lesions larger than 3 cm (sometimes for debulking, followed by sclerotherapy), with progressive growth, bone erosion, dyspnoea or dysphagia [6]. It is also advocated for the resection of remaining fibrotic tissue after sclerotherapy or as a first-line therapy for lesions outside the cervico-facial region, associated with few intraoperative risks or aesthetic sequelae [7]. Minor complications include lymphorrhea, keloids, dehiscences, fistulas, and the need of a prolonged post-operative drainage from the wound, with an associated risk of infection[8].

The aim of the study was to review and discuss the non-surgical strategies for the management of cervical lymphangiomas, with particular attention to the sclerosing agents.

II. MATERIAL AND METHODS

All relevant articles including "cervical lymphangiomas" or/and "sclerotherapy" were searched on PubMed, Cochrane and Embase platforms. Inclusion criteria were: (1) studies published mostly within the last fifteen years, (2) studies including paediatric population, (3) studies reporting advantages, success rate, recurrence rate, complications and dose for each and every sclerosing agent, (4) studies written in English. In addition, instructions for the procedure of ultrasound or CT-guided sclerotherapy and other alternative treatments were considered.

III. RESULTS

As many as 47 articles dealing with sclerotherapy of cervical lymphangiomas in children were collected. Beside short information about the first therapeutical approaches, laser therapy, radiofrequency ablation and oral medications (e.g. Sirolimus) including the newest target-therapy, a much larger knowledge was obtained about sclerotherapy's rationale, steps and agents, from the most employed (OK-432, bleomycin/pingyangmycin, doxycycline, sodium tetradecyl-sulphate) to potential alternatives (such as ethanol) or occasionally-used substances (e.g., acetic acid, Ethibloc, Tissucol, Polidocanol).

IV. DISCUSSION

Historically, the first non-surgical treatments for cervical lymphangiomas were with simple direct drainage, aspiration and radiation. A combined radio-chemotherapeutic approach was performed in selected cases of hemolymphatic malformations [1].

Laser therapy is an alternative to surgery for small and superficial (cutaneous or oral) lymphangiomas or for debulking of invasive, large and non-excisable lymphangiomas. Traditional techniques consist of the resection and removal by photocoagulation with argon, carbon dioxide, Nd:Yag, KTP and diode lasers. Pain, oedema and swelling are associated with complete healing at 6-8 weeks, although a scar may persist for many years. Ten to 33% of cases are complicated by intraoperative bleeding or nerve injury. Namour and coll suggested a peculiar therapeutic method for debulking of invasive and extensive lesions within oral soft tissues, preventing the patients from mutilation. A CO2 laser machine with output power of 2W in defocus and in non-contact mode for at least 3 min is used, with a distance between the laser handpiece and the tissular impact point around 6 cm, the delivered focal point at 0.3 mm, the effective spot diameter range at tissue at about 2 cm (power density = 0.63W/cm2) and the estimated energy density range at 114.65–191 J/cm2. This protocol does not cause disintegration/vaporisation but only overheating, with subsequent fibrous healing. Out of seventeen patients, only three (18%) experienced recurrence and no major complication (embolism, infection or mutilation) occurred. Other minor treatments include cryotherapy, diathermy and electro-cautery [9].

Another example of local treatment is offered by radio-frequency ablation (RFA) or hypothermic ablation, destroying lesions at lower temperatures (40-70°) with subsequent lower damages within surrounding tissues. Micro-cystic lymphangiomas in mouth, throat, pharynx, retro-pharynx and tongue may benefit from RFA, which also helps to stop accidental or intra-operative bleedings [10].

Sclerotherapy is nowadays largely employed in case of macro-cystic or mixed lymphangiomas, where the size of the cysts allows them to be punctured and a wider distribution of the agent is achieved. However, OK-432, bleomycin and above all doxycycline have recently proved effective also with micro-cystic variety [2]. The rationale comes from the observation that lymphangiomas can reduce their size or regress after a spontaneous infection, probably due to the destruction of the epithelium, reduction of lymph production and collapse of the cyst: thus, the idea of adopting sclerosing agents to mimic such an effect. Puncture of

the dominant cyst (or more, in case they are non-communicating) with a fine needle (20 G or more) is followed by aspiration (in order to enhance the SA effect) and injection, in one or more times, of the sclerosing agent, using the same amount as the aspirated fluid (if impossible, half of the lesion's volume). It can be repeated in case of partial response or whenever more administrations are chosen, each session being separated by weeks up to a month. General or loco-regional anaesthesia is preferred in children or uncooperative patients and in adults or small cystic malformations, respectively; the patient's position is changed many times to favour a uniform distribution of the agent and the treatment lasts up to two hours. A postoperative compressive bandage is advised in order to increment the time of contact between the solution and the cyst's wall and to prevent seroma formation, bleeding or effusion of the SA. The procedure can be performed under ultrasound or CT: the first is cheaper, more available, does not employ ionising radiations (thus being advisable in children and young adults), defines better the different components within the lesion, grants different cranio-caudal angles and reduces the risk of accidental puncture of large blood vessels; however, it is operator-dependent and offers a narrow field of view, with the risk of missing some important findings, especially at the post-procedure check. CT instead is easier to perform and provides a more panoramic view but implies radiation and the needle path to lie on the axial plane with its full length [1]; a detailed example of this procedure is offered in *figure (patient) 4,* whereas *figures (patients) 5 and 6* show examples of successful outcomes comparing lymphangiomas before and after sclerotherapy. Fluoroscopic guidance is also reported, especially in case of the most superficial lesions, with the possibility to inject contrast medium into the lesion in order to highlight communications between the intra-lesional spaces and establish the amount of SA to be used [4]. Complications include intraoperative bleeding (due to their dysplastic nature), accidental injuries to nerves, vessels, organs and other tissues (due to extravasation), peri-lesional fibrosis and aesthetic sequelae (due to necrosis followed by second-intention reparation), dose-dependent cardio-pulmonary toxicity (especially with bleomycin) and acute respiratory insufficiency (with large lymphangiomas undergoing inflammation, necrosis and quick volumetric expansion); the latter could be managed with dexamethasone or, preferably, avoided by splitting the treatment in more sessions [7]. An example of follow-up program would consist of a clinical examination after one to three weeks, ultrasonography after six to twelve weeks and then (depending on the results of ultrasound) MRI, unless evidence of early recurrence or any other complication occurs [8]. A review by Adams et al didn't prove the superiority of sclerotherapy over surgery but showed it was the treatment of choice in most major paediatric vascular anomaly centres: surgery was reserved for refractory cases, with sclerosing agents not improving either clinics or aesthetics, micro cystic lesions or those associated with life-threatening airway obstruction. Nowadays there are no worldwide-accepted guidelines and patient selection seems to guide the choice. In addition, neither surgery nor sclerotherapy can guarantee complete healing with just one session: it is actually advisable to perform multiple treatments or combine them[1].

When dealing with sclerotherapy, the first substances to be employed (with poor results) were boiling water, quinine, urethane, iodine tincture, nitromin, sodium morrhuate 5% and acetic acid 40 to 50%, the last two with little more reference in literature [1]: sodium morrhuate is currently employed for orbital lymphangiomas; acid acetic causes an area of coagulative necrosis much wider than ethanol (with pain and tingling sensation) but with a faster and more complete regression [11]. Many others sclerosing agents (SA) were used by the years, but no guidelines are currently available due to the infrequency of the disease and the limited studies; therefore, the decision is based on Centres and operators according to their experience and the availability and side-effects of the agents [12].

OK-432 (Picibanil; *table 1*) was first used by Ogita in 1987 [13]. It comes from the lyophilisation of a mixture of Streptococcus pyogenes and G-Penicillin. It favours the production of IL-1, IL-2, IL-6, INF-ɣ and TNF, the activation of neutrophils, macrophages, NK and T lymphocytes, the apoptosis of the epithelium and increases the permeability of the endothelium, accelerating the lymphatic fluid drainage. Compared to others SA, OK-432 is associated with a lower risk of extravasation and subsequent peri-lesional fibrosis, systemic toxicity or/and aesthetic sequelae [14]. In addition, according to both Efe and Hazim (2016), the lesion is still feasible for surgery even after sclerotherapy failure [15,16]. Luzzato et al (2000) confirmed its usefulness for residual and recurrent lesions, as well as the low invasivity and scarring [17]. Sichel et al (2004) agreed with the lack of a significant peri-lesional fibrosis [18]. The percentage of success is 50-92% (remaining high even with repeated injections), with 43% of complete and 29,3% of partial remissions [19], whereas the frequency of the recurrences is around 11% [15] and the complications are rare and mostly local (pain, heat, induration, erythema, oedema, swelling, aesthetic sequelae, swallowing difficulty and odynophagia, infections) with sporadic fever, sepsis and shock, especially in patients with allergy for G penicillin [1]. Yoo et al (2009) stressed the safety of OK-432, reporting minor complications only and stating a high long-term efficacy [20]. Rebuffini et al (2012) also reported anaemia and a transitory increase of platelets'

concentration [21]. The low systemic toxicity allows OK-432 to be used also with micro-cystic (where the percentage of success reaches nearly 50%) or intra-parenchymal components, where the risk of tissue absorption is the most [22]. Ruiz et al (2004) confirmed its feasibility for micro-cystic lesions, as well as those associated with a risk of airway obstruction [23]. Ogita recommends 0,1 mg/10 cc with a maximum of 20 mL of solution or 0,2 mg of substance [24]. Despite all its advantages and proven effectiveness, however, OK-432 is less and less employed in the UK.

Bleomycin sulphate *(table 2)* is an antibiotic with antitumour action, inhibiting DNA synthesis. Tanigawa et al were the first to employ it as a sclerosing agent, reporting a lower recurrence rate than surgery and stating the possibility to use it in case of surgery failure [25]. Sung et al also used it for debulking of unresectable lesions [26]. It shows good responsivity (88%), a discrete frequency of complete remissions (36-63%) and a low recurrence rate (15%), as sclerosing agent [27]. Zulfiqar et al (1999) confirmed it safety and effectiveness, especially when dealing with macro-cystic lesions [28]; a decade later, Sanldas et al (2011) confirmed a higher success when treating unilocular malformations [29]. Analogous outcomes, along with similar success rates, were obtained by Kurmar (2012) [30], Jain (2013) [31], Porwal (2018) [32] and Hashmi (2020) [33]. Orford et al (1995), obtained minimal surgical scars and declared a low risk of potential injury of nerves and/or blood vessels. Local signs of inflammation (restricted movement of the neck, pain, swelling, induration, stridor, difficulty in breathing or swallowing, intra-luminal bleed, infections) subside spontaneously within few days. Systemic effects range from mild (vomiting, diarrhoea. flu, local hyperpigmentation, hyperkeratosis and thickening of the skin) to anaphylaxis [34]. Mathur et al (2005) declared no major complication or mortality [35]; the same conclusion was drawn by Rozman (2010) [22]. Sporadic cases of pulmonary fibrosis actually occur only when high doses are employed (total administration of 400 U or single administration of 30 mg/mm^2), as during systemic chemotherapy or with renal clearance under 25-35 mL/min. Follow-up to monitor for pulmonary fibrosis is left to exercise tolerance and patients are also advised to avoid live vaccine for 3 months. The suggested dose is between 0,5 and 1 mg/kg with a maximum of 5 mg/kg [35].

Pingyangmycin or bleomycin A5 *(table 4)* is similar to common bleomycin (A2) but it is cheaper and determines less peri-lesional fibrosis and complications, with possible hair loss, gastrointestinal reactions, fever, rash. The recommended dose is 1 mL/cm^2 and must be lower than 8 mg per single injection and 40 mg in total. Jia et al. (2014) treated orbital and peri-orbital lymphatic malformations with PYM, with a mean volume decrease of 84% after a median number of 2 injections, and no

recurrences at 8 months were observed [12]. Gao (2002) employed it also with oral, maxillofacial and cervical lesions, considering it as a potential primary therapy [14].

Doxycycline *(table 3)* is a bacteriostatic antibiotic, which inhibits angiogenesis through the blockage of the production of metalloproteinases and vascular endothelial growth factor (VEGF) [10]. It is inexpensive, widely available and it has minimal side effects, including dental discolouration in children, allergic reactions [2], haemolytic anaemia, hypoglycaemia, neurological complications and rare cases of methaemoglobinaemia [36]. Pain, swelling, haemorrhage and cellulitis may occur, as well as scarring, skin excoriation and Horner's syndrome [2]. Complete or near complete response was achieved from the very beginning of its use, as reported from the experience of Cordes (2007) [37] and Nehra (2008) [38]. Later, Jeffrey Cheng (2015) performed sclerotherapy with doxycycline on a larger cohort of subjects, reporting an efficacy of 84.2%, and insufficient responses or recurrences in 33% [2]. The recommended dose varies between 20 and 150 mg at a concentration of 10 to 20 mg/mL [36]. Despite many Authors, such as Cahill (2011) [39] and Farnoosh (2015) [36], state its primary role for the treatment of large macro-cystic malformations, some others like Burrows (2008) declare an even higher efficacy than OK-432 in case of micro-cystic lesions [11]. Shields (2009) agreed with the former and employed it also in cases of post-surgical recurrences [40]. Shergill (2012) put together the theories from the previous authors claiming that doxycycline could be used for nearly all types (macro-cystic, micro-cystic or mixed) of lymphangiomas [41].

Despite the few quotations, sodium tetradactyl-sulphate or sotradecol 3% *(table 4)* is used in many paediatric centres in the UK as second like after doxycycline. It has shown to determine an average response of 80-90% (complete in 40%) and complication rate of 17% only, including swelling, oedema, mild allergic reaction, chronic facial pain, infections, cutaneous necrosis and nerve injury. Dose varies between 3 to 6 mL and its main indication remains orbital LM [25]. Farnoosh (2015) achieved similar results, with an even better outcome if combined with doxycycline [36].

Alcohol 98% *(table 4),* used for many arteriovenous malformations, causes rapid cellular dehydration and protoplasm precipitation. On one hand, it shows good therapeutic response (from 64 to 96%), large availability and low cost. On the other hand, it can determine unexpected damage within the surrounding tissues and, at high doses, severe systemic effects such as hypotension, respiratory depression, arrhythmias, seizures, hypoglycaemia and exitus. For this reason, low doses are employed (0,5-1 mL/kg), mostly associated with injuries of skin, mucosae and peripheral nerves

(7,5-27,95%) or thrombotic phenomena. Recurrence rate is around 30% [6]. Impellizzeri et al. (2010) reported their experience with CT-guided instillation of 5-15 mL of alcoholic solution with complete disappearance of the lesion in 7 patients, with only one needing a second injection. Only one patient experienced self-limiting erythema and tenderness and no recurrence was observed at 2 years [1]. Puig et al. affirmed that the use of ethanol for lymphatic malformations could cause the extravasation as a major risk. To avoid it, he proposed a double-needle procedure to limit the total volume of ethanol injected in order to reduce intra-lesional pressure and thus extravasation [42]. Ethanolamine oleate is obtained from a combination of an organic base with oleic acid and shows alcohol-like effect, although it has lower toxicity [12].

Although few experiences about the use of acetic acid at 30-50% *(table 4)* demonstrate a more rapid effect compared with the other SA and the frequent need for a single treatment session only, the extravasation into the nearby tissues represents a serious issue. As an example by Won et al, a patient with a cervico-mediastinal lymphangiomas experienced infiltration in the lung parenchyma surrounding the lesion [43].

Alcoholic solution of Zein (Ethibloc, *table 4)* contains Zein (a prolammine), diatrizoate sodium (radio-opaque marker), poppyseed oil and 96% ethanol. It is biodegradable, effective and safe, but the risk of scars, salivary fistulas, infections and the poor aesthetic results (30 days of trans-cutaneous elimination) have limited its use. The recommended dose is between 1 and 7,5 mL. M. A. Emran et al. reported satisfactory to excellent results in 84% of macro-cystic/mixed and in 77% of micro-cystic lesions and considered Ethibloc an effective alternative to surgery for macro-cystic lymphangiomas or post-surgical recurrences. Failure and subsequent recurrence rate seems around 23% [44].

Fibrin glue (Tissucol, *table 4*) is an expensive haemostatic agent making the cysts collapse, the dose being 10 to 15% of the suctioned volume; Castañon et al obtained complete remission of 8 of 9 monocystic neck lymphangiomas [45]. Polidocanol *(table 4)*, a local anaesthetic, is administered at the dose of 1 mL for each cm of lesion, does not need further anaesthesia and causes erythema with induration of the skin only; Jain et al achieved a volume reduction of 96% to 100% in 3 patients [46].

To the knowledge, some substances are administered orally in addition to local treatments and overseen by a physician in normal circumstances. Sirolimus or rapamycin is a mTOR-PI3K pathway inhibitor increasingly employed when surgery fails or is not feasible. It has been used for orbital lymphatic malformations and (later) conjunctival or superficial peri-ocular lesions [12, 47]. Other systemic treatments

include Cyclophosphamide (alkylating antineoplastic agent), interferon, steroids (promoting inflammation and cicatrisation respectively), isotretinoin, Bevacizumab, Thalidomide (anti-angiogenic), Alpelisib and TIE2 (targeted therapy against PIK3CA and tunica intima endothelial kinase 2), propranolol and sildenafil (relaxing smooth muscle thus causing cystic decompression and opening of secondary lymphatic spaces). The last one, a phosphodiesterase type 5 inhibitor used for erectile dysfunction and pulmonary hypertension, proved effective in reducing the number and severity of bleeding episodes, especially with macro-cystic and mixed lesions [12]. Newest target-therapies, appearing more effective with macro-cystic lesions, include PI3K inhibitors (LY294002, BYL719, wortmannin), AKT inhibitors (ARQ092, MK-2206), MAPK inhibitors, (U0126), multiple kinase inhibitors (sorafenib, trametinib), VEGF-A inhibitors (bevacizumab), BMP and Wnt modulators (dorsomorphin, LDN-193189 and calyculin A), JAK inhibitors (ruxolitinib), calcium channel blockers (amlodipine), KATP activators (minoxidil), zoledronic acid, interferon a 2b, prednisolone, sunitinib. However, large-scale studies are required in order to confirm efficacy and potential side-effects for each substance [10].

A recent review by Liu et al. (2021) confirms how, although surgery remains the first-line strategy for lymphangiomas (especially large lesions for possible complete removal), risk of scars, incomplete resection/recurrences and injury to blood vessels or cranial nerves (especially the submandibular branch of the facial nerve) is high. Thus, despite above-mentioned side effects like soft-tissue oedema and skin necrosis as well as variable recurrence rates, sclerotherapy may often represent the elective treatment; moreover, micro-cystic lesions appear more and more susceptible to SA like OK-432. However, since "single treatments" often achieve insufficient results, ongoing strategies tend to administer multiple therapies. For example, surgery may obtain debulking of large lesions, with remaining tissue being treated with sclerotherapy (e.g. bleomycin) and systemic drugs administered to alleviate the symptoms of pain and bleeding. Analogous strategies might be employed with superficial micro-cystic mucosal lesions, where RFA or laser-therapy plays the main role. Moreover, oral medications themselves may be used prior to surgery and/or sclerotherapy. However, further studies are necessary in order to promote univocal guidelines; thus, to date, as already stated by Liu et al., "individual therapies" (also including target-therapy) represent the most appropriate strategy in the treatment of lymphangiomas, with no exception for cervical lesions [10].

V. Conclusion

Treatment of cervical lymphangiomas represents a rare but challenging issue. Despite the wide range of treatments discussed, cervical lymphangiomas remains a relatively infrequent finding. Thus, a limited number of studies is reported in literature and small cohorts of patients are considered, with subsequent difficulties in performing a reliable meta-analysis about the efficacy of any single treatment.

Despite the lack of worldwide-accepted guidelines, our research highlights the role of sclerotherapy as the first-line non-surgical strategy because of the lower rates of aesthetic sequelae, recurrence, complications (e.g. injury to blood vessels or cranial nerves) and mortality and the better course, so that it might represent a valid or equivalent alternative to surgical therapy. Moreover, the two treatments can be used in combination (e.g. when remaining lymphangiomatous or fibrous tissue is present) or sclerotherapy can prove more efficient (e.g. micro-cystic lesions when using OK-432). Sclerosing agents should usually be employed with macro-cystic lesions, and no substantial difference is reported in terms of efficacy from a SA to another, all of them ranging from about 60 to 90% in different studies. Although no longer used in several countries (including the UK), OK-432 would be optimal for its minimal extravasation (and thus peri-lesional fibrosis and aesthetic sequelae), the lowest rate of both local and systemic complications and recurrences (around 10%) and, eventually, the feasibility with either micro-cystic lesions. Bleomycin can represent a valid option as long as low doses are administered, due to the well-known risk of pulmonary fibrosis; the issue is partially solved when employing pingyangmycin which is still, however, indicated mostly for peri-ocular lesions. Doxycycline is more available, cheap and apparently even more efficient than OK-432 in cases of micro-cystic lymphangiomas; as an alternative, we suggest tetradactyl-sulphate. Despite its wide availability and low cost, the higher risks of neurovascular/visceral injuries (about 10 to 30%), systemic side effects and recurrences (around 30%) make ethanol a definitely second-line treatment.

However, several considerations must be made. Firstly, multicentric prospective studies are necessary in order to better evaluate this technique and define the best sclerosing agent to be used. Secondly, as already mentioned, ongoing strategies tend to combine the above-mentioned treatments (including oral medications and the newest "target-therapies") according to each patient's characteristics and lesions (as well as psychological aspects), giving rise to a multi-faceted approach.

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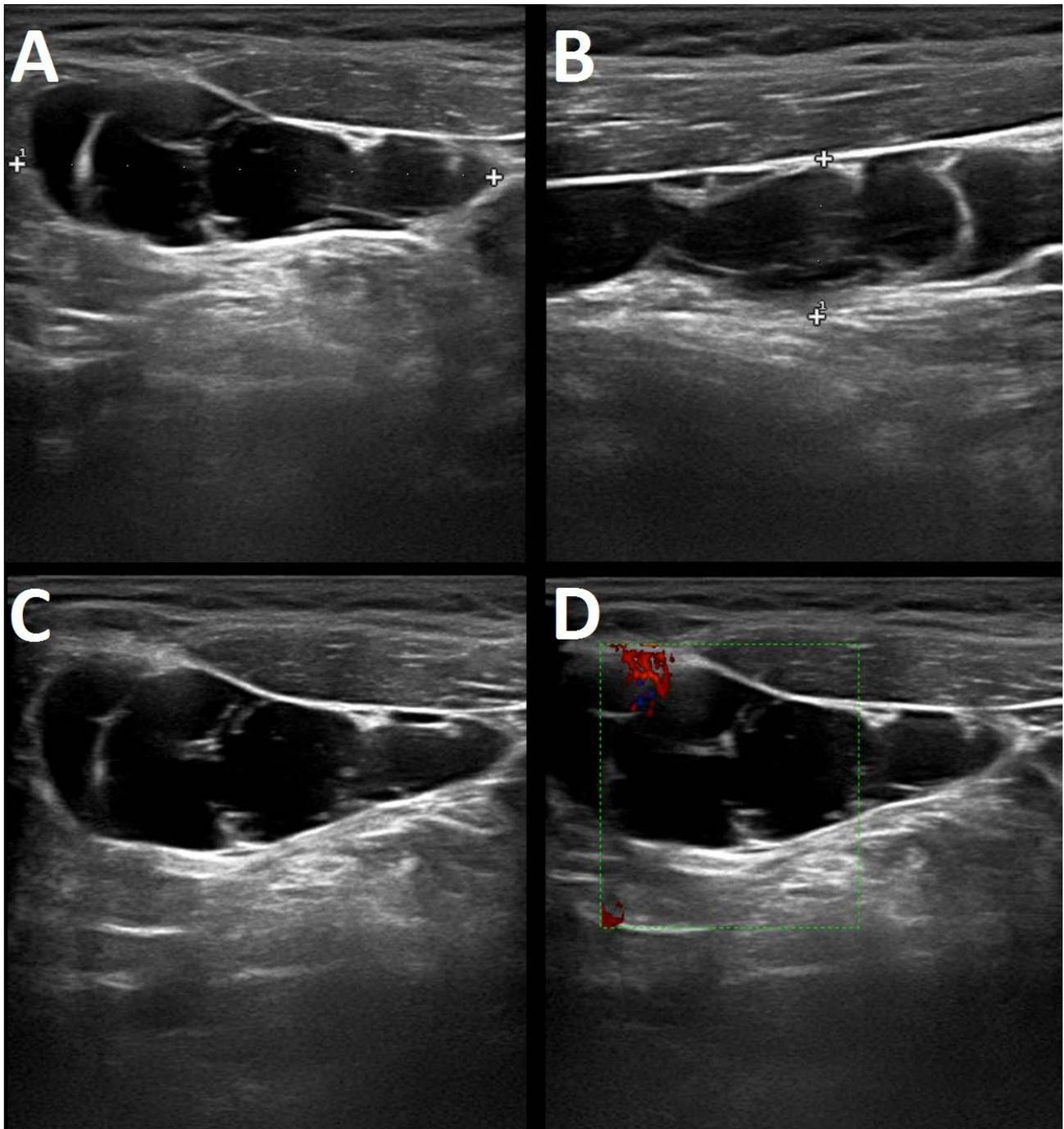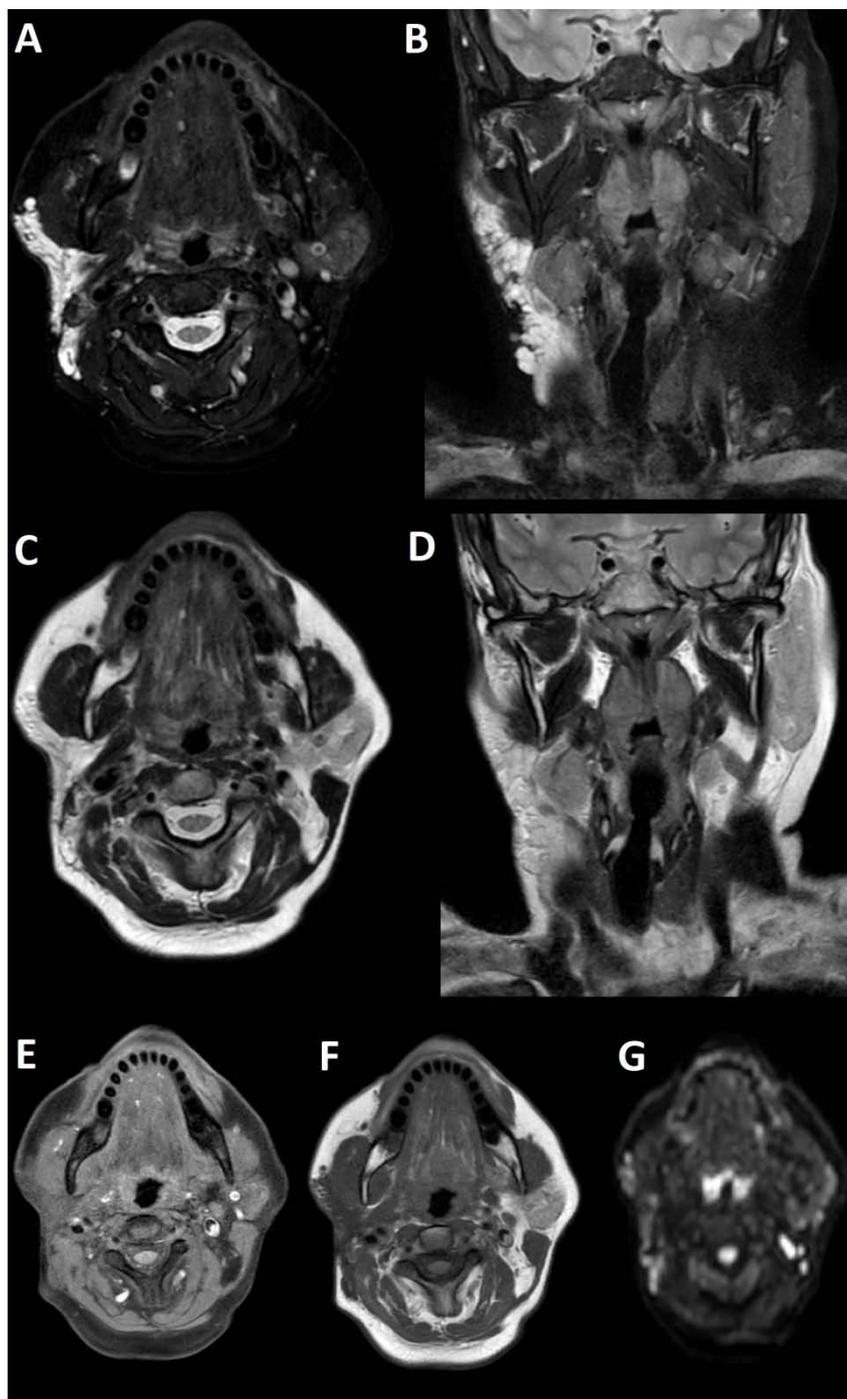
Figure/Patient 1

A 7 year-old girl presenting with a tumefaction at the level of the right latero-cervical region. US scans show a 43x14 mm subcutaneous fluid formation with septa extending from the root of the neck to the submandibular region (**A-B**). Doppler-mode demonstrates lack of blood flow within the lesion or the septa (**C-D**). Diagnosis of cystic lymphangioma is done.
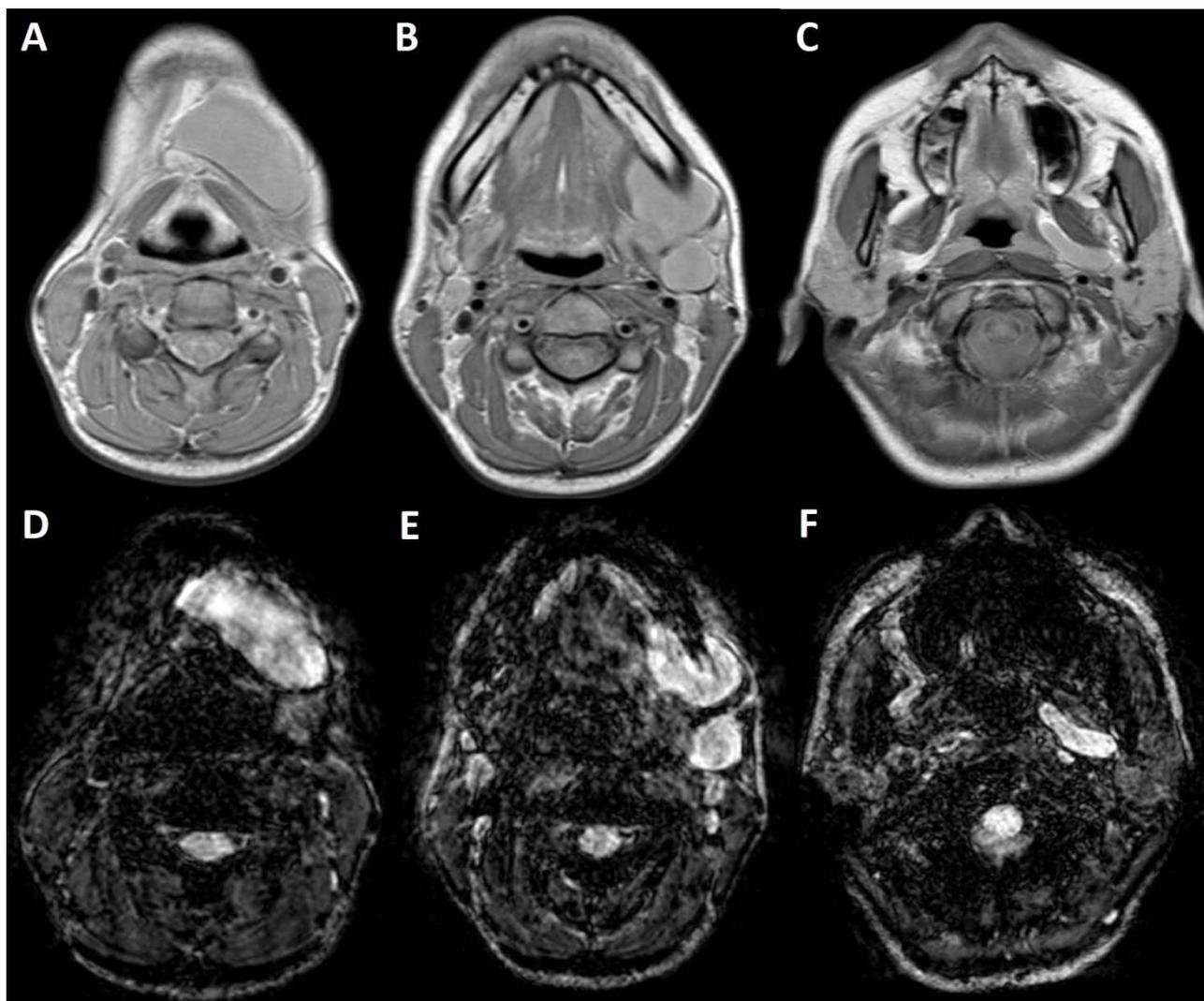
Figure/Patient 2

A case of right mandibular lymphangioma in a 10 year-old boy, hypoechoic with some septations and no blood vessels (**A**) and hyper-intense on T2 axial (**B**) and coronal (**C**) MR scans.

Figure/Patient 3

An 8 year-old girl with prior surgical excision of a right latero-cervical lymphangioma presenting with a new-onset tumefaction within the same region. MRI scans show a 9-10 cm subcutaneous multilocular lesion, extending between two virtual planes crossing the retro-molar trigone and the thyroid respectively, with deep invasion of para-pharyngeal spaces cranially and the space between the submandibular gland and the vascular peduncle of the neck caudally. The lesion appears hyper-intense on T2 weighted scans with (A-B) and without (C-D) fat suppression, hypo-intense on T1 weighted scans with (E) and without (F) fat suppression and hyper-intense on DWI scans with high B values (G). Diagnosis of loco-regional recurrence of cystic lymphangioma is done.

Figure/Patient 4

1. A 7 year-old girl presenting with a tumefaction at the level of the left latero-cervical region. MRI scans show a subcutaneous lesion occupying the left submandibular, parotideal, para-pharyngeal and part of the masticatory spaces. The lesion appears slightly hyper-intense on T1 (**A-C**) and markedly hyper-intense on T2 (**D-F**) scans. Diagnosis of cystic lymphangioma is done.
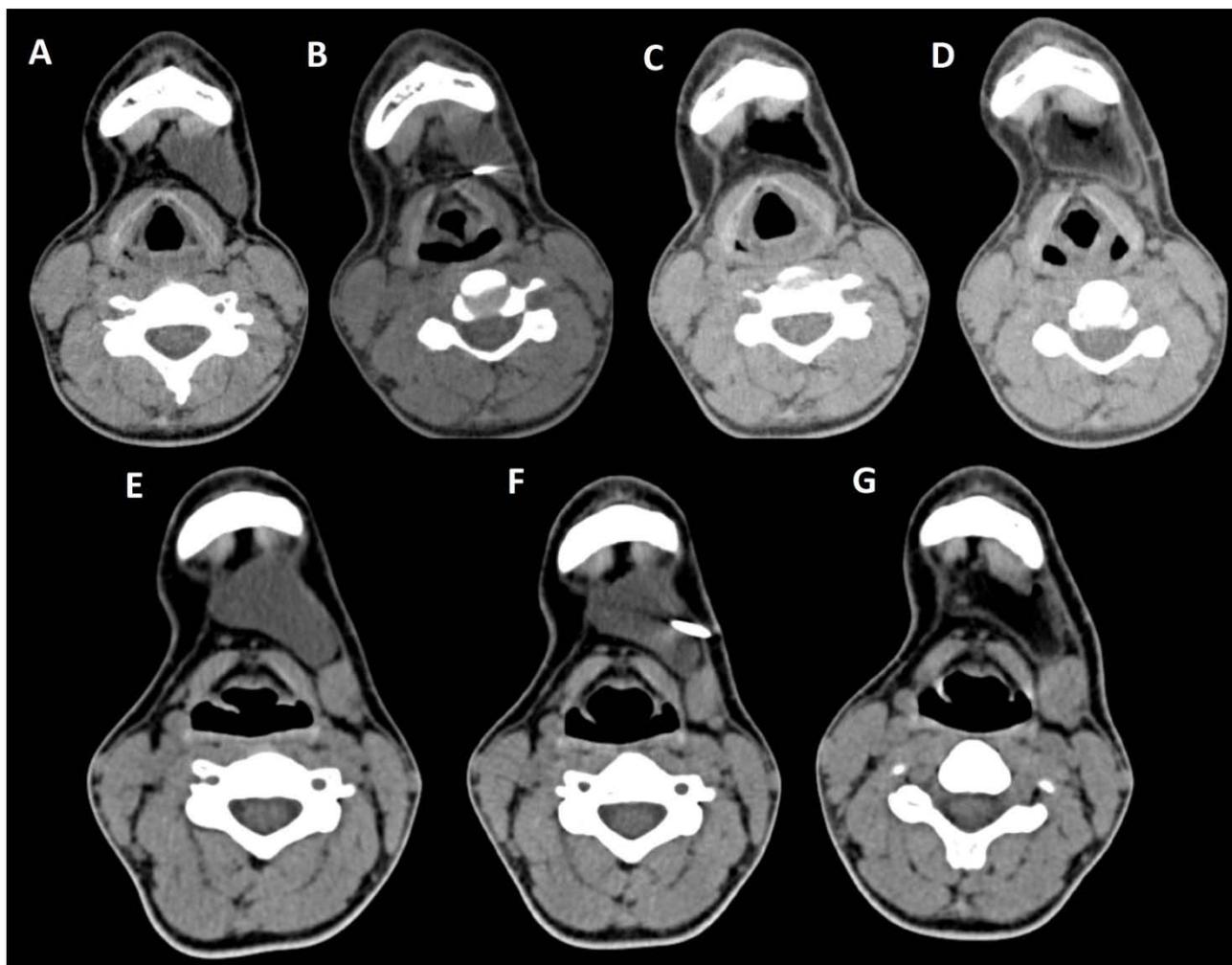
2. The same patient undergoing two different sessions (**A-D** and **E-G**, respectively) of sclerotherapy with absolute ethanol. An 18-G needle is introduced into the lesion and about 10 cc of citrine-turbid fluid are aspirated (**B** and **F**). Then, 5 cc of ethanol are injected and the patient is mobilised in order to distribute the SA throughout the lesion (**D** and **G**). The patient is dismissed and a one-week antibiotic therapy is prescribed.
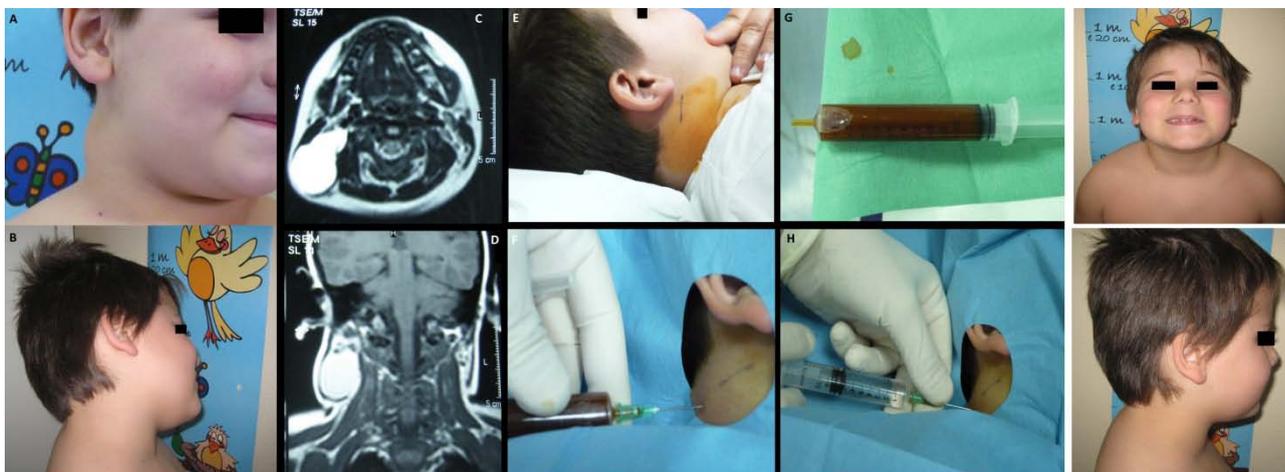
Figure/Patient 5

A 6 year-old boy presenting with a right latero-cervical tumefaction (**A-B**): axial (**C**) and coronal (**D**) MR scans show an expansive subcutaneous formation with high T2-signal, consistent with lymphangioma. The patient is demanded for sclerotherapy with ethanol: after disinfection and sterilisation of the skin (**E**), a fine needle is introduced into the lesion (**F**) and a yellowish viscous fluid is aspirated (**G**); then, alcohol is injected into the lesion (**H**). No recurrence is visible at two months-follow up (**I-L**).
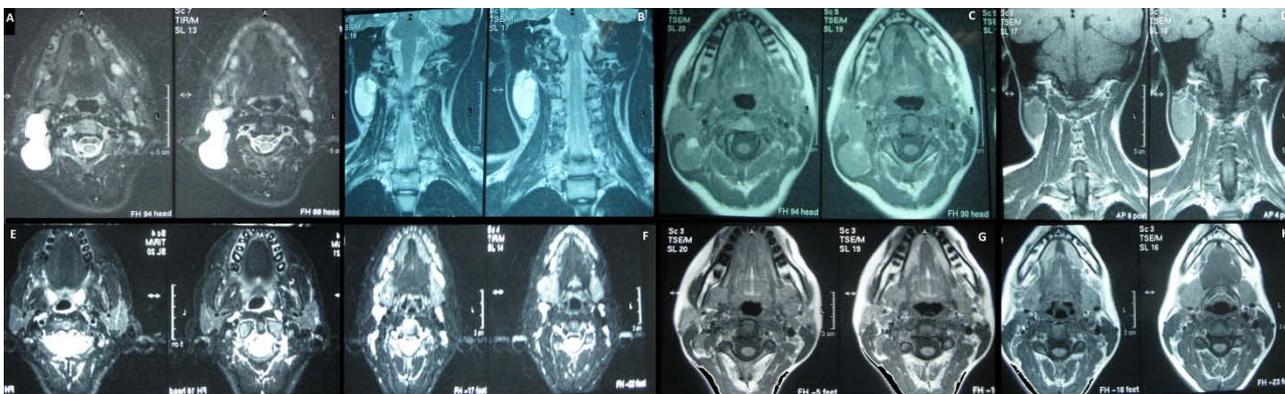
Figure/Patient 6

Another case of a right latero-cervical lymphangioma in a 8 year-old boy, markedly hyper-intense on T2 axial (**A**) and coronal scans (**B**) and slightly hyper-intense on T1 axial (**C**) and coronal (**D**) MR scans. The patient is demanded for sclerotherapy with ethanol: no recurrence is visible at the follow-up MR T2 (**E-F**) and T1 scans (**G-H**).

Table 1: Data from literature about OK-432

	Advantages	Success rate	Recurrence rate	Complications	Dose
Ogita S. et al (1987) [13]	Low toxicity, immuno-stimulating effect	89% (total: 9 patients)	11%	Local inflammation, fever	As much as aspirated by mixing each 0.1 mg with 10 cc distilled water, not exceeding 0.2 mg on total; next injection at 3-4 week
Luzzatto G. et al (2000) [17]	effective for primitive, residual and recurrent lesions, low invasivity and scarring	Excellent results in macrocystic, good and poor in 25% and 75% of mixed type (total: 11 and patients respectively	9.1%	Fever, signs of local inflammation, cervical swelling needing a feeding tube	0.1-0.2 mg/dose (one to 16, average 3)

Ruiz E. et al (2004) [23]	significant volume reduction also in microcystic lesions, feasible when there is risk of airway obstruction	complete remission in 63% (prevalently macrocystic), partial response (50 to 70%) in 27% (prevalently mixed); (total: 19 patients)	None	Fever, erythema, oedema, infection	(see Ogita) One to eight administrations
Sichel et al (2004) [18]	No perilesional fibrosis	complete or sub complete resolution in 73%, no response in 27% (total: 11 patients)	9.1%	Local inflammation, fever, odynophagia	0.01 mg/mL of the lesion's fluid, with a maximum of 0.2 mg in the first injection and 0.3 mg in the second or third injections
Yoo et al (2009) [20]	only minor complications, high long-term efficacy	Short term (83.5%) and long-term (76.3%), varying from macrocystic (92%) to microcystic (62%), from unilocular (94%) to multilocular (64%), from below (77.8%) to above mylohyoid muscle (21.7%) or mixed (20.3%); (total: 55 patients)	42% after first administration, lower in the next	Neck discomfort, swallowing difficulty, disfigurement of face, dyspnoea	(see Ogita) One to five administrations
Rebuffini E. et al (2012) [21]	No perilesional fibrosis, good response to additional treatments	Complete remission in 53.33%, marked reduction in 33.33%, moderate response in 13.33% (total: 15 patients)	12.5%	pain, redness, induration, fever, anaemia, transitory increase of platelets' concentration	0.2 mg per session (one to three), each separated by 6 months
Efe N. et al (2016) [15]	Minimal extravasation and damage of nearby tissues, does not preclude further surgery	66% for microcystic lesions, almost 100% for macrocystic lesions	12%	Local pain, heat, oedema, anaemia and rare penicillin allergies	(see Ogita)
Hazim et al (2016) [16]	Minimally invasive, little scar, does not interfere with subsequent surgery	Complete remission in 16.66%, marked reduction in 50%, mild reduction in 16.66% and no response in in 16.66% (total: 6 patients)	None within responding lesions	Fever	0.01 mg/m in one to eight administrations

Table 2: Data from literature about Bleomycin

	Advantages	Success rate	Recurrence Rate	Complications	Dose
Tanigawa et al (1987) [25]	Less recurrences when compared with surgery, feasible after surgery failure	excellent results in 53%, good results in 47% (total: 15 patients)	none	Swelling, fever, vomiting, diarrhoea, local infection, dyspnoea	0.3 to 0.5 ml, once every 4 to 6 weeks, microsphere in-oil emulsion
Sung et al (1995) [26]	feasible with unresectable lesions (debulking)	complete or nearly complete shrinkage 40%, marked reduction in size in 30%, partial or minimal reduction in 30% (total: 10 patients)	None within responding lesions	local swelling and inflammation, pneumonia of uncertain origin	1 mg/mL, from 3 to 7 sessions
Orford et al (1995) [34]	low risk of neurovascular damage, no surgical scar	excellent results in 45%, good in 36%, no response in 18% (total: 11 patients)	9%	fever, vomiting, cellulitis, skin discoloration	0.3 to 0.6 mg/kg
Zulfiqar et al (1999) [28]	Safe and effective, especially in macrocystic lesions	excellent results in 36%, good in 45%, no response in 18% (total: 11 patients)	None in short-term	none	0.5 mg/kg from 1 to 4 sessions
Mathur et al (2005) [35]	no major complications, no mortality	complete or near complete response in 30%, good response in 70% (total: 10 patients)	30% (70% residual disease)	local swelling and inflammation	1 mg/kg with a maximum of 6 mg/kg, every 2 weeks, in a solution of 1 mg/ml in large lesions and 2 mg/ml in smaller lesions.
Rozman et at (2010) [22]	Safe and effective, no major complication when using normal doses	Complete resolution in 63%, good response in 21% and poor response in 16% (total: 22 patients)	8%	Swelling, stridor, difficulty in breathing or swallowing, pain, tenderness, erythema	0.5 mg/kg with a maximum of 5 mg/kg, from one to six sessions
Sandlas et al (2011) [29]	Safe and effective with unilocular lymphatic malformations	significant response in 53.33%, good response in 33.33% poor response in 13.33% (total: 15 patients)	None within responding lesions	fever, swelling, skin discoloration	0.6 to 0.8 mg/kg
Kumar et al (2012) [30]	Safe and effective	excellent response in 20%, good in 74.29%, poor in 5.71% (total: 35 patients)	None within responding lesions	fever, transient increase in size of swelling, local infection, intraluminal bleed, skin discoloration	0.5 mg/kg body weight, no more than 10 units at a time

Jain et al (2013) [31]	Safe and effective with macrocystic	Complete response in 100% (total: 8 patients)	None in short-term	Fever, erythema	0.6 mg/kg, from one to three sessions
Porwal et al (2018) [32]	Safe and effective with macrocystic lesions, no major complications	Complete resolution in 62.5%, good response in 25%, poor response in 12.5% (total: 8 patients)	None within responding lesions	Fever, erythema, pain , restricted movement of the neck, abscess	0.5 mg/kg, from one to three sessions
Hashmi S et at (2020) [33]	Safe and effective, especially with macrocystic lesions	Excellent results in 20%, good results in 72.5%, poor results in 7.5% (total: 31 patients)	None within responding lesions	Post-procedural swelling, fever, local tenderness, skin changes	0.3 IU/kg, from one to three sessions

Table 3: Data from literature about doxyclicline

	Advantages	Success rate	Recurrence Rate	Complications	Dose
Cordes et al (2007) [37]	readily available, inexpensive	Resolved or marked reduction in all patients (total: 12 patients)	None within responding lesions	Swelling, haemorrhage into the cystic cavity	10 mg/mL
Nehra et al (2008) [38]	readily available, inexpensive	Complete response in macrocystic lesions, partial response in mixed lesions (total: 11 patients)	18%	None	10-mg/mL up to a maximum of 200 mg
Burrows et al (2008) [11]	Effective, safe, few complications	Excellent response in macrocystic (90%), good in combined (80%) and in microcystic (60%) lesions (total: 41 patients)	None within responding lesions	pain and swelling, skin blisters, hair loss, Horner's syndrome	10 mg/mg, with a maximum dose of 1000 mg or 20 mg/kg, from 1 to 6 administrations
Shiels et al (2009) [40]	Feasible for primary lesions (even microcystic) or post-surgical recurrences	Excellent response in 90% (total: 17 patients)	13%	Cellulitis, haemorrhage into cysts	20 mg/mL, one to four sessions
Cahill et al (2011) [39]	Feasible for large macrocystic head and neck lymphatic malformations	Excellent response in 65%, good in 23%, poor in 12% (total: 17 patients)	None within responding lesions	emolytic anaemia in 2 infants, hypoglycaemic and metabolic acidosis, transient hypotension, skin excoriation, delayed neural complications, Horner's syndrome, transient left lip weakness, right facial nerve palsy and left hemidiaphragm paralysis	10 mg/mL with a dose range of 50 to 500 mg

Shergill et al (2012) [41]	Safe and effective with all types of lesions	Excellent or satisfactory response in 90% (total: 14 patients)	None within responding lesions at short-term	respiratory distress, pain, swelling, cosmetic deformity, leakage from the skin, Horner's syndrome	10mg/mL with a maximum of 300 mg in patients under 12 and 1200 mg in patients over 12
Cheng (2015) [2]	inexpensive, widely available, minimal side effects	84.2% with 60.5% after the first session (total: 38 patients)	Not available (patients lost to follow-up)	Tooth discoloration, allergic reactions, haemorrhage into cysts, cellulitis, pain, increased swelling, scarring, skin excoriation, Horner's syndrome	10mg/mL with a maximum of 20mg/mL
Farnoosh et al (2015) [36]	Safe and effective, especially with macrocystic and mixed lesions	complete resolution in 50%, satisfactory improvement in 25%, poor response in 25% (total: 29 patients)	None within responding lesions	infection, exacerbation of the lesion, jaw pain, facial swelling	10 mg/ml, ranging from 20 to 150

Table 4: Data from literature about other sclerosing agents

	Advantages	Success rate	Recurrence rate	Complications	Dose
Pingyangmicin (Jia et al, 2014) [12]	feasible for orbital or periorbital malformations	marked improvement in 76%, moderate in 18% (total: 33 patients)	none within responding patients	swelling of the conjunctiva, localized subcutaneous atrophy	1 mL/cm^2, be lower than 8 mg per single injection and 40 mg in total
Pingyangmicin (Gao et al, 2002) [14]	could be the primary therapy for oral, maxillofacial and cervical lesions	curative in 100% of cystic, 46.36% of capillary, 16.16% of cavernous and 19.05% of mixed capillary and cavernous lesions (total: 195 patients)	none within responding patients	mild and local	5 mg to 70 mg and 5 to 58 times, 1 time per 2-4 weeks
Alcohol 98% (Impellizzeri et al, 2010) [1]	large availability and low cost	100% (total: 8 patients)	none at 2 years	erythema and tenderness (if high doses are employed: hypotension, respiratory depression, arrhythmias, seizures, hypoglycaemia, exitus)	5-15 mL of solution, each but one needing one session only

Sodium tetradecyl-sulphate (Farnoosh et al, 2015) [36]	feasible for orbital lesions	complete resolution in 60%, satisfactory to poor response in 40% (total: 29 patients)	none within responding patients	tongue swelling, bleeding, difficulty chewing, oedema, mild allergic reaction, chronic facial pain, infections, cutaneous necrosis, nerve injury	3 to 6 mL
Acetic Acid (Won et al, 2004) [43]	Effective, no serious complications (if no systemic absorption occurs)	Complete resolution in 60%, good resolution in 40% (total: 5 patients)	none	pain	2 to 5 mL
Ethibloc (Emran et al, 2006) [44]	Safe, effective and biodegradable	satisfactory to excellent results in 84% of macrocystic/mixed and in 77% of microcystic lesions (total: 35 patients)	none within responding patients	scars, salivary fistulas, infections, aesthetic sequelae	1 to 7,5 mL
Tissucol (Castanon et al, 1999) [45]	Excellent long-term results and few complications	Remission in 89% (total: 9 patients)	11%	none	10% to 15% of the suctioned volume
Polidocanol (Jain et al, 2002) [46]	Safe, painless, effective	Remission in 100% (total: 3 patients)	none	superficial erythema, induration of the skin	1 to 6 mL, in 1 to 20 injections