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Image-Guided Percutaneous Bleomycin and Bevacizumab Sclerotherapy of Orbital Lymphatic Malformations in Children

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Abstract
Purpose To evaluate the effectiveness and safety of image-guided percutaneous sclerotherapy using bleomycin for macrocystic and bevacizumab (Avastin^{TM}) for microcystic orbital lymphatic malformations in children.
Materials and Methods Between October 2015 and July 2018, we prospectively evaluated 10 pediatric patients who presented clinically and radiologically with lymphatic malformations and were treated with percutaneous sclerotherapy. Patients with venous malformations were excluded. Eight females and two males with ages ranging from 3 to 17 years (mean: 8.8, SD: 4.9) were included. Guided with ultrasound and fluoroscopy, macrocysts were treated with bleomycin instillation. For microcystic components in three patients, bevacizumab was injected intralesional. All patients underwent ultrasound and non-contrast MRI to evaluate response to treatment after 6 weeks.
Results The malformations were macrocystic in seven patients and complex (macro/microcystic) in three. Twenty sclerotherapy sessions were performed, (range: 1–3 sessions, mean: 2, SD: 0.8). Clinically, there was a significant reduction in the proptosis after treatment ($P = 0.007$) and dystopia ($P = 0.018$). The local radiological response showed a reduction in the maximum lesions diameters and volumes after treatment ($P = 0.005$ and 0.005, respectively). Two of the three patients treated with bevacizumab showed a reduction in the lesions volumes by 90.4% and 63.4%, respectively, whereas one patient did not show volume reduction. Transient periorbital edema and ecchymosis occurred following the procedure with no major complications encountered. Follow-up ranged from 9–33 months, mean: 20.3, SD: 7.4.
Conclusion Bleomycin sclerotherapy is a safe and effective treatment for orbital macrocystic lymphatic malformations. Further use of bevacizumab for microcystic lesions in a larger series is required to outline its efficacy and safety.

Keywords Orbital vascular malformations · Sclerotherapy · Bleomycin · Bevacizumab

Introduction

Orbital lymphatic malformations (OLMs) are rare low-flow vascular anomalies representing 1–4% of all orbital lesions, primarily seen within the first decade of life [1, 2]. Lesions can be classified as macrocystic (> 1 cm), microcystic (< 1 cm) or lesions with mixed morphology. The cystic lesions may be communicating and contain serous or hemorrhagic fluid. Lymphatic malformations (LMs) associated with various portions of venous components especially in complex and deep lesions, so-called lymphaticovenous malformation (LVM) [3–5].

Orbital lesions may be superficial in the conjunctiva, involving the eyelids that might lead to disfigurement, or

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located deep in the orbit even surrounding the optic nerve complex leading to proptosis and globe displacement and thus causing problems such as amblyopia, optic nerve compression, diminished visual acuity and exposure keratitis. Previous studies have shown that inappropriate therapy may cause reduced vision in approximately 40% of patients and blindness in 7% of cases [2, 5].

Management of OLMs has always been a challenge due to the infiltrative nature of the lesions. A conservative approach is preferred in small asymptomatic lesions. Surgical debulking with partial or total excision has been used to relieve compression of the optic nerve, relieve pain, preserve ocular alignment and improve cosmetic appearance, yet surgery is difficult with high risk of hemorrhage, collateral damage, postoperative cicatrization and recurrence [6, 7].

Percutaneous sclerotherapy has been increasingly used as a less invasive alternative for the management of OLMs with promising results. Several case reports and series have utilized sodium tetradecyl sulfate (STS), bleomycin, OK 432 (Picibanil), oxytetracycline, doxycycline, ethanol, pingyangmycin and sodium morrhuate 5% with variable clinical outcome [8]. In this series, the aim was to evaluate the effectiveness and safety of ultrasonographic and fluoroscopic guided sclerotherapy using bleomycin for macrocystic and bevacizumab (Avastin^{TM}) for microcystic OLMs in children.

Materials and Methods

Between October 2015 and July 2018, a prospective consecutive case series was conducted on 10 pediatric patients with unilateral OLM. Patients below 18 years who presented with disfiguring and functionally threatening proptosis with or without dystopia and were diagnosed clinically and radiologically with OLMs were included. Patients with known hypersensitivity to bleomycin, impaired renal or pulmonary function and patients with venous malformations or those who were lost to follow-up were excluded. Eight females (80%) and two males (20%), ranging in age from 3 to 17 years (mean: 8.8 years), were included. The study was performed after obtaining the consents of their legal guardians and the approval of the local institutional review board.

Preprocedural Evaluation

Patients underwent an ophthalmological assessment, ultrasound and a contrast-enhanced MRI before treatment. Full ophthalmological assessment was undertaken, including fundus examination, refraction, intraocular pressure and extra-ocular motility. The degree of proptosis and dystopia was measured using a ruler. The visual acuity was measured using the logarithm of minimum angle resolution best-corrected visual acuity (log MAR BCVA).

Ultrasound was performed to assess the extent and accessibility of the lesion for percutaneous puncture, to differentiate between the cystic and solid components and to evaluate the vascularity of the solid components. Macrocystic LMs typically appear as anechoic spaces divided by septa, whereas microcystic LMs appear hyperechoic owing to their small cavity size. Ultrasound is also useful for evaluating prior hemorrhage and demonstrating fluid–fluid levels. In addition, Doppler examination of LMs demonstrates no flow through the lesion, which helps distinguish them from VMs [3].

Contrast-enhanced magnetic resonance imaging was performed to evaluate the location, size, extension, signal intensity and pattern of contrast enhancement of the lesion. LMs appear as multi-loculated cystic masses with fluid signal intensity and no flow voids. Macrocystic lesions usually demonstrate low signal intensity on T1 weighted images (WIs), high intensity on T2 and STIR WIs and may be septated. Internal fluid–fluid levels are common, whereas microcystic lesions display an intermediate signal on T1 WIs and an intermediate to high signal on T2 WIs. LMs typically do not enhance after contrast injection unlike VMs [3, 9].

Sclerotherapy Technique

All cases were performed under general anesthesia by an interventional radiologist. The periocular region was prepared using 5% povidone–iodine solution, and an antibiotic ophthalmic gel preparation (Fusidic acid) was instilled in the eye. All patients received a single dose of IV dexamethasone (0.25 mg/kg) on induction.

Under ultrasound guidance, superficial cysts were punctured with a 21 Gauge butterfly needle, while deep intraconal cysts were punctured with a less traumatic 22 G spinal needle or cannula. In deep or intraconal lesions, especially in mild proptosis and a narrow window for the needle entry, the needle is introduced parallel to the bony wall, without trials to displace the globe, and once reaching the retro-orbital space, the needle tip is redirected toward the lesion (Fig. 1). Partial aspiration of the cyst was performed avoiding cyst collapse and malposition of the needle tip. This was followed by slow injection of 1–2 ml of contrast medium (Omnipaque 240, GE Healthcare, Oslo) under fluoroscopy and digital subtraction, in different projections, to ensure the absence of vascular communication and contrast leakage. The same amount of injected contrast was aspirated again to allow space for the sclerosing agent. Then bleomycin (Fresenius Kabi USA LLC, Lake Zurich, Illinois) 0.25 IU/kg was instilled under US

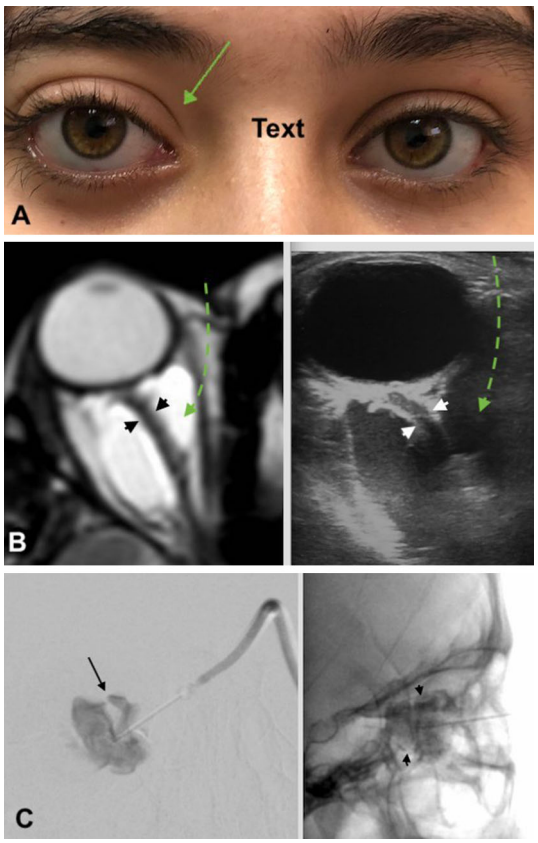


Fig. 1 Technique of percutaneous sclerotherapy: **A** Clinical photograph of a 15-year-old girl presenting with headache mild proptosis for 5 years duration (arrow points to the puncture site during sclerotherapy). **B** Axial MRI T2 WIs and ultrasound image of the right orbit, demonstrating a macrocystic intraconal OLM surrounding the optic nerve complex and displacing it medially (arrowheads). It displays bright T2 fluid signal intensity on MRI and hypo-echogenicity on ultrasound. (Arrows demonstrate the direction of the needle to reach the intraconal space. **C** Digital subtraction angiography image (AP projection) and X-ray cross-table (lateral projection) after injection of 2 ml contrast medium using 22 G spinal needle. Note the dispersion of the contrast medium around the optic nerve complex (arrow) and the posterior extension of the macro-cyst (arrowheads). This was followed by instillation of 3 ml (6 IU) bleomycin

control in small volumes < 3 ml/session, at concentration 2 IU/ml. The bleomycin volume and dose were decreased in small lesions (Figs. 2, 3).

In three patients with mixed LMs, after bleomycin injection of the macrocysts, the microcystic components were injected with 1.25 mg Avastin (Bevacizumab, Genentech/Roche), prepared in an insulin syringe 0.05 ml solution. Under ultrasound guidance, a 22 G spinal needle was introduced into a solid portion of the lesion. Without aspiration or contrast injection, the drug was injected slowly and monitored by ultrasound.

Postprocedure Follow-Up

Patients were admitted for observation for 24 h and underwent ophthalmological assessment immediately after the procedure and prior to discharge. Analgesics, systemic antibiotic (penicillin with clavulanic acid syrup), oral steroid (chlorpheniramine and dexamethasone syrup) or prednisolone tablets (1 mg/kg/day) for older children, with gradual withdrawal over one month, and a topical antibiotic-steroid combination (Tobramycin—dexamethasone eye ointment) were prescribed. The patient was instructed to use ice packs for the first two days then hot foments till the resolution of the lid edema.

Clinical assessment was scheduled on weekly basis for monitoring of any complication. Measurements of the proptosis, dystopia and visual acuity were taken 6 weeks after sclerotherapy.

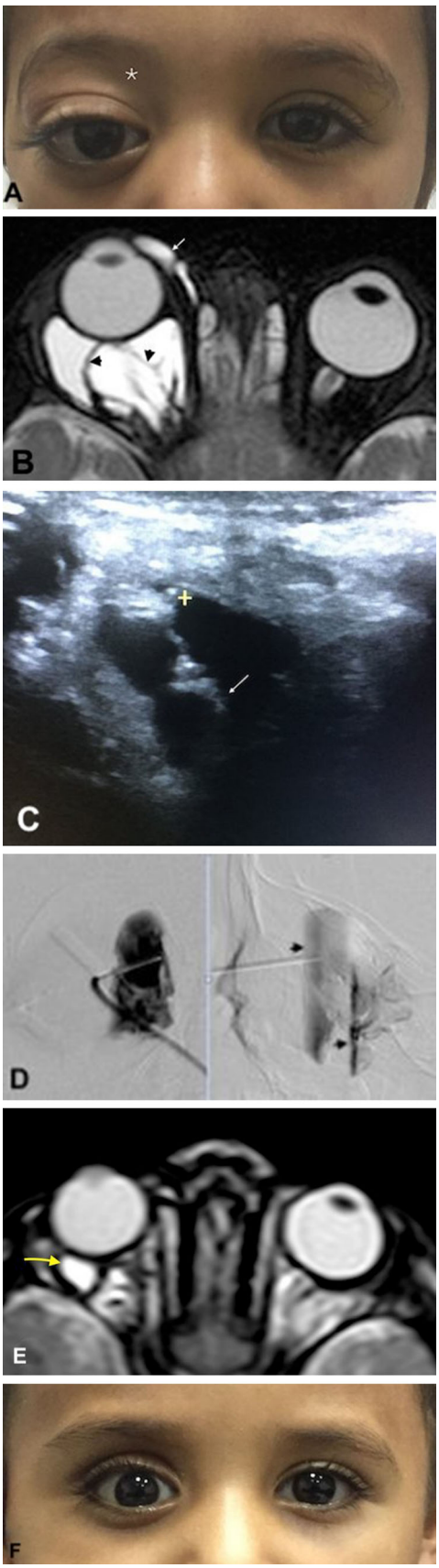
Radiological assessment was done using ultrasound and non-contrast MRI after 6 weeks of sclerotherapy. To evaluate the local response to treatment using MRI measurements, the maximum lesion diameters and volumes were calculated before treatment and 6 weeks after the last session. Lesion volumes were calculated with the ellipsoidal volume formula: Volume = (length $\times$ width $\times$ height $\times$ 0.523). All residual macro- or microcystic components, as well as residual fibrotic components, were included in the measurements. For the microcystic components injected with bevacizumab, measurements were taken for the whole lesions as well as for the microcystic components separately. Sclerotherapy procedures were repeated at 8-week intervals, depending on the clinical and radiological response.

Results

Ten patients were diagnosed with unilateral OLM based on the clinical and radiological examination. All patients presented with proptosis, six patients with inferior dystopia, eight patients with limitation of ocular motility and two patients with amblyopia. Two patients had undergone a previous surgical biopsy.

The OLMs were purely macrocystic in seven patients, and complex macro-/microcystic in three. Lesions were located deep (retro-orbital) in three patients, superficial (preseptal) in one patient and six patients had superficial and deep components. Two patients had additional extra-ocular extension in the cheek and infratemporal fossa.

Patients underwent repetitive sclerotherapy sessions, with a total of 20 sessions for the 10 patients (range: 1–3, mean: 2, SD: 0.8). Bleomycin dose ranged from 2.5 to 6 unit/session (mean: 3.5, SD: 1.7). The clinical and



◀**Fig. 2** Four-year-old boy presenting with progressive right-sided proptosis since birth with limited ocular motility and history of episodes of acute orbital swelling following trauma. **A** Clinical photograph showing right-sided proptosis and infero-lateral globe displacement. (Asterisk points to the puncture site in the first sclerotherapy session), **B** Axial MRI T2 WIs with fat suppression, demonstrating large retro-orbital macrocystic multi-locular LM, with small preseptal component (arrow), it displays bright T2 signal intensity with low signal internal septae (arrowheads), **C** US image taken during puncture of the medial macrocystic component using a 22 G spinal needle (arrow). **D** Digital subtraction angiography images (AP and lateral projections) after injection of 2.5 ml contrast medium, showing multi-locular, medial cystic component, not communicating with the lateral compartment of the lesion and showing fluid–fluid levels (arrows), with no leakage or vascular connection. This was followed by instillation of 3 ml bleomycin (2.5 IU). **E** Axial MRI T2 WI after three sclerotherapy sessions treating different compartments, showing small residual intraconal cystic component (arrow) with regression of the proptosis. **F** Clinical photograph taken 2 months after three sessions, showing considerable clinical improvement

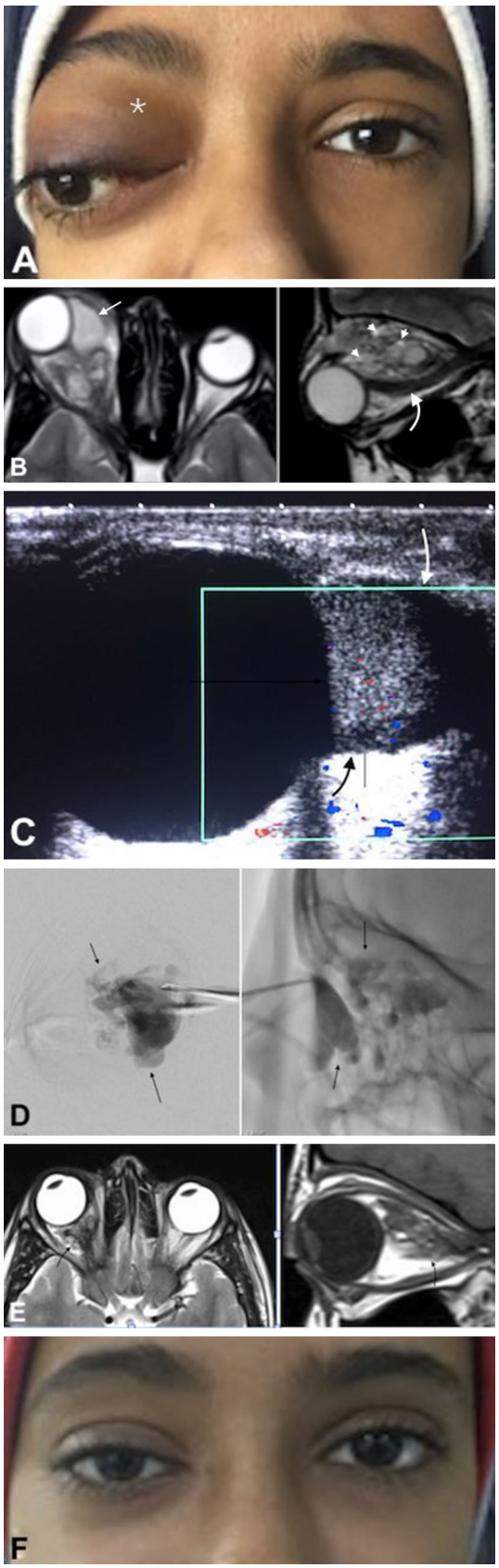
radiological follow-up ranged from 9 to 33 months (mean: 20.3, SD: 7.4).

The treatment protocol was well tolerated by all patients, with only minor transient side effects that occurred in all patients in the form of pain, edema, and ecchymosis of the periorbital area for a few days after injection. No major complications were encountered.

Clinical response: The degree of proptosis ranged 1–18 mm (mean: 5.9, SD: 4.95) and inferior dystopia ranged 2–9 mm (mean: 4.2, SD: 3.5). Both showed significant reduction 6 weeks posttreatment, for proptosis ranging 1–10 mm (mean: 3.2, SD: 3.2) and for dystopia ranging 0–5 mm (mean: 2.2, SD: 1.98), ($P = 0.007$) and ($P = 0.018$), respectively. There was an improvement in the ocular motility in all patients. There was no significant difference between the visual acuity (log MAR BCVA) before and after treatment.

Radiological response: The maximum lesions diameters ranged 12–52 mm (mean: 33.4, SD: 12.9), and lesions volumes ranged 3.7–45.2 ml (mean: 18.5, SD: 17.4). There was significant reduction in the max lesion diameters 6 weeks posttreatment ranging 10.3–35 mm (mean: 20.6, SD: 8.38) and volumes ranging 0.4–18.5 ml (mean: 3.7, SD: 5.9) ($P = 0.005$ and 0.005, respectively). The initial and posttreatment clinical and radiological data are summarized in Table 1.

Three patients were treated additionally with intralesional bevacizumab injection. The total lesions volumes were 29.7 ml, 11.2 ml and 45.2 ml. The microcystic components represented 21%, 29.5% and 40% of the total lesions volumes, respectively. There was reduction in the total lesions volumes posttreatment by 37.8%, 76.8% and 81.7%, respectively. Two patients showed a significant reduction in the microcystic lesions volumes by 90.4%



◀**Fig. 3** Thirteen-year-old girl presenting with progressive right-sided proptosis for 5 years duration, together with limited ocular motility, diminished visual acuity and amblyopia. **A** Clinical photograph showing right-sided proptosis and infero-lateral globe displacement. (Asterisk points to the puncture site). **B** MRI axial and sagittal T2WIs demonstrating complex retro-orbital and preseptal LM of the right orbit, causing proptosis and inferior displacement of the optic nerve (curved arrow). The largest macro-cyst is seen at the superior medial aspect of the orbit (arrow). The microcystic component showed numerous tiny small cysts (arrowheads). **C** Doppler US image of the medial macrocystic component (arrows), demonstrating hypo-vascular cyst and containing high-level echogenic fluid (hemorrhagic), **D** Digital subtraction angiography image (AP projection) and X-ray cross-table (lateral projection) after injection of 2.5 ml contrast medium, showing multi-locular macrocysts with fluid levels and no leakage or vascular communication (arrows). Bleomycin 3 ml (4 units) was instilled in the macrocystic component, then bevacizumab 1.25 mg was injected in the microcystic component. **E** MRI axial T2WIs and sagittal T1WIs after two sessions of sclerotherapy showing marked reduction in the size of the lesion with residual intraconal low signal intensity fibrous tissue (arrows). **F** Clinical photograph taken 6 months after the second session, showing clinical improvement

after two injections and 63.4% after a single injection, whereas one patient did not show volume reduction in the microcystic component after a single injection.

One patient with extensive complex LM in the orbit, cheek and infratemporal fossa showed partial recurrence of the clinical symptoms. This patient showed an initial improvement of the proptosis for 6 month, after three sclerotherapy sessions, using bleomycin for the macrocystic lesions and bevacizumab (injected once) for a retro-orbital microcystic component. At 11 months follow-up, the proptosis recurred with no change in the size of the microcystic component, whereas the macrocystic components previously injected did not recur back, other residual lesions that was not injected had increased in size. The patient was scheduled for a debulking surgery.

Discussion

The treatment approaches to OLMs have changed in the past two decades toward the use of minimally invasive sclerotherapy owing to the infiltrative nature of such lesions. Surgical excision is challenging and often incomplete especially in lesions occurring in the posterior orbit, with a high risk of complications and postoperative recurrence. On the other hand, sclerotherapy may make subsequent surgical excision easier by reducing the size of the lesion [7, 10].

A wide variety of sclerosing agents have been used in the management of LM without strong evidence that anyone agent is advantageous over the others. STS is a commonly used sclerosing agent in OLMs with proved efficacy

Table 1 Initial and posttreatment clinical and radiological results

	No of patients	Range	Mean	SD	*P* value
Proptosis pretreatment (mm)	10	1–18	5.9	4.95	
Proptosis 6 weeks posttreatment (mm)	10	1–10	3.2	3.2	0.007
Dystopia pretreatment (mm)	6	2–9	4.2	3.5	
Dystopia 6 weeks posttreatment (mm)	6	0–5	2.2	1.98	0.018
Initial max. lesions diameter by MRI (mm)	10	12–52	33.4	12.9	
Max. lesions diameter 6 weeks posttreatment (mm)	10	10.3–35	20.6	8.38	0.005
Initial lesions volume by MRI (ml)	10	3.7–45.2	18.5	17.4	
Lesions volume 6 weeks posttreatment (ml)	10	0.4–18.5	3.7	5.9	0.005

and safety [11–17]. Other sclerosing agents such as bleomycin, OK 432, oxytetracycline, doxycycline, ethanol, pingyangmycin and sodium morrhuate 5% have been used in a few case reports with good clinical and radiological outcomes [18–28]. Reported complications include transient pain, periorbital edema and increase intraocular pressure, whereas hemorrhage has been reported in few cases [11, 13, 25, 27].

Bleomycin is an established anticancer cytotoxic drug, found to be useful as a sclerosing agent for LVM. Its mechanism of action in vascular malformations is explained by induction of an inflammatory response, endothelial destruction and then stromal fibrosis, which may explain the initial and transient enlargement of the lesions shortly after injection [29, 30]. In this series, bleomycin was chosen as a sclerosing agent because it is readily available to our practice and the experience with its use in LVMs elsewhere in the body. It has proven high efficacy, minimal inflammation and low rate of complications in extra-orbital lesions [29–32]. Reported complications include mild flu-like symptoms, erythema, edema and skin pigmentation, whereas systemic complications such as lung toxicity have not been reported after treatment of LMs probably because of the local injection and low doses used [31].

Bleomycin use in OLM was also encouraging; Shen et al. [18] reported two cases with OLM that showed total resolution and improvement of proptosis after bleomycin sclerotherapy. Gooding and Mayer [19] reported four cases that showed significant regression and marked clinical improvement with no systemic or ocular side effects. Paramasivam and colleagues [20] reported 22 cases of OLM, of which 16 were treated with bleomycin, volume reduction $> 80\%$ was achieved in 57% of cases and reduction of 50–79% in 43% with no severe complications. Hamroush et al., in their study on 17 patients, reported a significant reduction in lesions volume $P = 0.001$ and proptosis ($P = 0.0117$) and four patients showed improvement of visual acuity. They reported severe periorbital edema in 76.5%, eyelid pigmentation in one patient, elevated IOP in three patients and severe conjunctival edema in one patient. Hanif et al. [23], in their study on eight patients, reported an average improvement of proptosis of 65% and ocular mobility in 87.5% patients. Raichura et al. [22] reported a dramatic response after bleomycin use in 13 cases and none of the patients experienced recurrence or significant complication.

In using this agent for orbital lesions, the primary challenge was to ensure a safe access to the retro-orbital space where ultrasound and fluoroscopy with digital subtraction proved sufficient for radiological guidance. To minimize the local inflammatory response to the drug and to reduce complications, low doses of bleomycin (less than 0.5 IU/kg) and small volumes (less than 3 ml) were utilized, a single needle puncture for each procedure and avoiding excessive probing and manipulations. Also patients were treated in multiple sessions to manage multilocular lesions. With this technique and regimen, a significant clinical response was achieved with reduction in the proptosis ($P = 0.007$) and the dystopia ($P = 0.018$) with improved ocular motility in all patients. Also, there was a significant reduction in the maximum lesions diameters and volumes 6 weeks posttreatment ($P = 0.005$ and 0.005, respectively). There were no major complications or bleeding that required further surgical intervention. Meanwhile, all the local inflammatory reaction was adequately managed with steroids on induction, postprocedural steroids, antibiotics and local fomentations.

Bevacizumab, the active ingredient of Avastin (Genentech/Roche), is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits vascular endothelial growth factor (VEGF) and inhibits the binding of VEGF molecules to its receptors on the surface of endothelial cells reducing angiogenesis and vascular permeability [33, 34]. It has been FDA-approved as a chemotherapy drug for the treatment of metastatic colorectal cancer and has been used

(off-label) in ophthalmology to treat choroidal revascularization secondary to age-related macular degeneration, diabetic macular edema and macular edema due to retinal vein occlusions with low complications, as its use was in healthy non-cancer patients and with lower doses of the drug than the intravenous dose [35–37].

To our knowledge, bevacizumab has not been used before in treating orbital vascular malformations. Its effect in reducing the vascular angiogenesis and the promising results from the local delivery of the drug by intravitreal injection in macular edema prompted us to investigate the effect of its intralesional injection of in microcystic OLMs. The same dose approved for intravitreal injection was used, though higher doses may be also safe and more effective.

Despite the favorable radiological response in two out of the three patients treated with bevacizumab with reduction in volume of the microcystic lesions by 90.4% and 63.4%, these results are somewhat confounded by the concurrent administration of bleomycin during the same treatment sessions and an argument could be made that bleomycin may have had at least a contributory effect on the final outcome. Such would be the argument if both components were in communication and in view of the low doses of bevacizumab administered. The few number of cases in general and those injected with bevacizumab in particular is the main limitation of our study, also the lack of information regarding the "safe" orbital injection dose compared to that for intraocular use.

In conclusion, intralesional bleomycin therapy in low doses over multiple sessions is a safe and effective treatment for children with macrocystic OLMs. In addition, bevacizumab therapy for microcystic lesions yielded preliminary promising results in this small cohort of patients. Larger series within which isolated injection of microcystic components and additional dose adjustments would be required to further outline its efficacy and safety.

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Compliance with Ethical Standards

Conflicts of interest On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Ethical Standards All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all legal guardians of the children.

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