Original Article

Management of macrocystic lymphatic malformation at uncommon site with aqueous bleomycin sclerotherapy

ABSTRACT

Introduction: Lymphangioma are rare vascular malformation that results from maldevelopment of primitive lymphatic sacs. They are most frequently found in the neck and axilla, while intra-abdominal and mediastinal lymphangiomas are uncommon. Atypical site of cystic hygroma in pediatric age group are usually difficult to diagnose clinically but can be diagnosed easily by ultrasound. The aim of the study was to evaluate the result of the intralesional bleomycin for macrocystic lymphatic malformation (LM) presenting at atypical site

Material and Method: All patients of LM of other than head& neck, axilla and abdomen presenting in pediatric age group were included in the study. Mainstay of diagnosis was ultrasound and was supplemented by CT scan wherever required. All patients were managed with intralesional bleomycin (ILB) and surgical excision was done only if primary therapy failed.

Result: Total 15 cases of LM presenting at atypical sites were included in the study. Series include two case of cystic hygroma of breast, 4 cases of cystic hygroma of anterior chest wall, two case of substernal LM, three cases of LM of parotid gland, one case of inguinal region cystic hygroma and 4 cases involving submandicular area. Complete resolution was observed in 13 out of 15 cases, and two cases had less than 50% reduction in size and were managed with surgical excision after second session of ILB.

Conclusion: Aqueous Intralesional bleomycin is a cost effective alternative to surgery even at rare sites of LM which provide better aesthetic outcome, and avoids complication associated with surgery.

Keywords: Cystic lymphangioma, sclerotherapy, ultrasound

INTRODUCTION

Macrocystic lymphatic malformation (LM) is a congenital malformation of the lymphatic system occurring in approximately 1 in 6000–12,000[1] births. Most macrocystic LMs are evident at birth (50%–65%), while remainders were evident by the age of 2 years. The head and neck is the most common site of occurrence of these lesions constituting 75% followed by axilla. Tongue, retroperitoneum, mesentery, groin, and pelvis are rare sites. Very rarely, it may be found in the parotid, arm, chest wall, breast, and substernal areas. Traditional management of cystic hygroma is surgical excision, but due to high complication rate and recurrences after surgery, intralesional sclerosing therapy is the preferred treatment. Till date, surgical excision is the treatment of choice for macrocystic LM presenting at rare sites; we are presenting nonsurgical management of these lesions using intralesional bleomycin (ILB).

MATERIALS AND METHODS

All cases of macrocystic LM presented in the Department of Pediatric surgery from July 2012 to July 2019, managed by a single surgical unit, were included in the study

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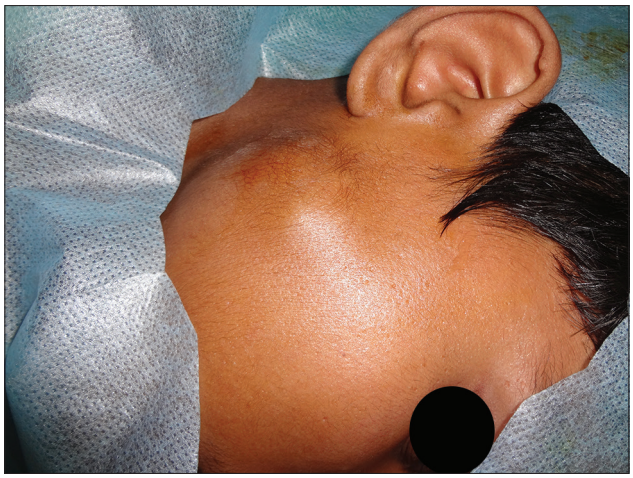

Figure 1: Soft-tissue mass in the parotid region

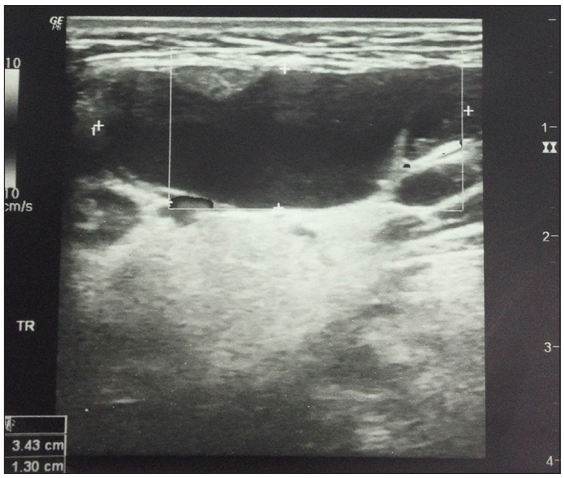

Figure 2: USG showing Cystic lesion in the parotid area

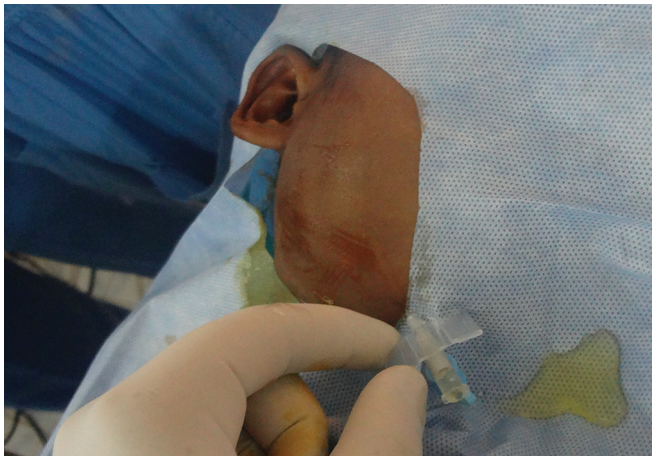

Figure 3: Aspiration of the cystic lesion under ultrasound guidance

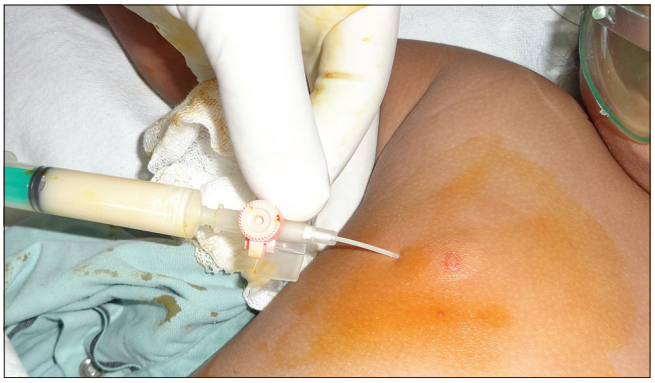

Figure 4: Aspiration of chylous fluid from the breast on the neonate

after taking ethical clearance from the Institute Ethical Committee (2020-157-IP-EXP-21). Owing to the unusual site of the lesion, clinical examination [Figure 1] alone was not sufficient for diagnosis; hence, ultrasound with color Doppler was the mainstay for diagnosis [Figure 2] which was supported by computed tomography (CT) scan if required. Patients who had achieved adolescence or had any history of trauma or surgery at the site of the lesion were excluded. LM with multiple microcyst was also excluded from the study. The patients of macrocystic LM involving common sites such as head and neck and axilla were excluded from the study. The diagnosis was made on the ultrasonographic feature and the fluid content of the lesion [Figure 3 showing serous fluid and Figure 4 showing chylous fluid]. In all cases, the site of the involvement, size, and volume of the lesion were meticulously documented based on ultrasound.

All cases were managed with ILB under ultrasound guidance in operation theatre with adequate sedation/pain relief/general anesthesia depending on the site of lesion and age of the patient. Bleomycin aqueous solution was used as sclerosing agent at concentration of (3 mg/ml) with a maximum dose not exceeding 0.3–0.5 ml/kg of body weight per session after aspirating content and postoperative compression of the site was done for 6–12 h where ever it was possible. The intravenous antibiotic was used for 24 h, followed by oral antibiotics and analgesics for 3 days. The duration between two sessions at our center is 6 months, and all cases were followed for 18 months before assessing the result. Reduction in size of >90% was considered as complete resolution [Figures 5-7], incomplete resolution if the reduction in size is between 50% and 90% and nonresponder if the reduction in size is <50% of the initial size.[2,3] In the present series, the evaluation of the lesion was mainly based on the ultrasound finding because, in more than half of cases clinical evaluation was not possible. Ultrasound was done by a single consultant and was evaluated by two senior radiologists after 18 months of the first ILB session.

RESULTS

A total of 15 cases were included in the study. The site of the lesion, size of the lesion, age of presentation, and nature of the fluid aspirated is compiled in Table 1. The

Table 1: Age of presentation, site and type of lesion, and treatment offered

Age and sex of patient	Site of cyst	Number of cyst	History of bleed/infection	Session of ILS with bleomycin	Complication	Response
2 months/male	Left breast	1	No evidence of infection or bleeding. Aspirated fluid was chylous in nature	Single session	Fever, subsided after 3 days	Clinically no obvious lesion seen, on ultrasound small cystic lesion was seen which was not amenable to aspiration
13 years/male	Right parotid [Figures 1-3]	1 macrocsyts with multiple microcsyts	History of pain and fever before presentation. Aspirated fluid was scanty and hemorrhagic in one and turbid in other cyst	Two session	Mild fever and pain subsided by its own	Minimal change after two sessions (<20% reduction in size), ultrasound done after second session showed micocsyts which were not amenable for aspiration: Considered as nonresponder and was treated surgically
5 months/male	Right BREAST [Figure 4]	1	None, clear fluid	Single session	None	Lesion not appreciated clinically, ultrasound showed almost complete resolution of the lesion with small hypodense residual lesion
9 years/male	Right parotid	1 macrocsyts with multiple microcsyts	History of pain and fever before presentation. Aspirated fluid was scanty and hemorrhagic in one and turbid in other cyst	Two session	Mild fever and pain subsided by its own	Almost 90% reduction after second session with small lesion left which was not amenable for IBL
5 years/female	Left breast	Multiple small cyst with two marocyst	History of pain in the breast 1 month back and it was the presenting complaint	Two session	Mild fever	Mild decreases in the size of lesion (<50% reduction) and was surgically excised
1 year/male	Anterior chest wall [Figures 5 and 6]	1macro cyst with few small cyst	None, aspirated fluid was clear	Single session	Fever and excessive cry needed analgesics for 3 days	>90% of resolution with no apparently visible lesion
10 years/male	Right submandibular area	Two macro cyst	None aspirated fluid was slight turbid	Two session	Pain and induration at the site of IBL	Around 90% reduction in size on ultrasound
5 years/female	Left parotid	3 macrocsyts and few microcsyts	History of infection at the time of initial presentation managed with intravenous antibiotics and ILS done after 1 month, aspirated fluid was turbid	Two session	Mild fever	>90% of resolution with small cystic lesion which was almost completely resolved after 2nd session of ILS with small fibrotic mass
7 years/female	Anterior chest wall	2 macrocsyts	None, each cyst had small amount of clear fluid	Single session	None	Regressed almost completely
13 years/male	Right parotid	1 macrocsyts with multiple microcsyts	History of pain and fever before presentation. Aspirated fluid was scanty and hemorrhagic in one and turbid in other cyst	Two session	Mild fever and pain subsided by its own	Minimal change after two sessions (<20% reduction in size), ultrasound done after second session showed micocsyts which were not amenable for aspiration: Considered as nonresponder and was treated surgically
7 years/male	Left parotid	4 macrocsyts and few microcsyts	History of infection at the time of initial presentation managed with intravenous antibiotics and ILS done after 1 month, aspirated fluid was turbid	Three sessions	Mild fever	>90% of reduction in size of two cyst while third cyst was properly seen at the time of second session. In second session IBL done in two cyst as one cyst was not amenable for aspiration due to very small size. After third session small lesion was seen which was not amenable to IBL

Contd...

Table 1: Contd...

Age and sex of patient	Site of cyst	Number of cyst	History of bleed/infection	Session of ILS with bleomycin	Complication	Response
9 years/female	Substernal lesion (not visible clinically) it was ultrasound finding	2 macrocysts	History of fever and pain in the lesion at presentation, initially managed with intravenous antibiotic for 7 days, intralesional sclerotherapy was done after 2 weeks. Aspirate was turbid	Single session	Fever, pain	Lesion was almost completely regressed on ultrasound done after 6 months with small residual cystic lesion which was not amenable to aspiration
18 years/male	Right upper chest	One large cyst (containing 300 ml of fluid)	No history of trauma but history of sudden increase in size in the last 2 years	3 session	Mild induration at the lesion	Almost 95% reduction size after 3rd session
4 year/female	Anterior chest wall	3 macro cyst	None, each cyst had small amount of clear fluid	Single session	None	Regressed almost completely with very small residual fibrotic lesion (not seen on inspection)
3 years/male	Right inguinal area	2 macro cyst with few microcyst	Occasional complaint of pain	Two session	None	>95% reduction after the 2nd session with very small residual fibrotic lesion

ILS: Intra Lesional Sclerotherapy

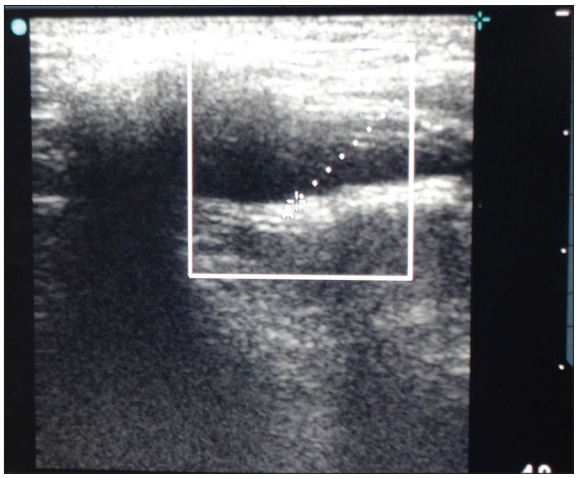

Figure 5: Ultrasound showing lesion is resolved

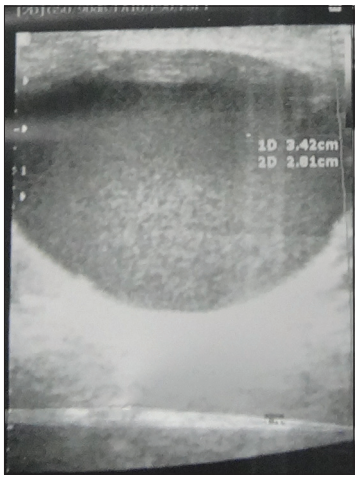

Figure 6: Ultrasound of the lesion of the breast

age of presentation ranged from 3 months to 18 years. Male-to-female ratio was 2:1. The number of lesions, history of infection or bleeding, number of sessions, and responses are tabulated in Table 1. Complete resolution was observed in 13 out of 15 cases, and two cases had <50% reduction in size and required surgical excision after the second session of ILB.

DISCUSSION

LMs are most commonly located in the cervicofacial region and axilla and contain single or multiple cysts. Communication with normal lymphatic channels is rare. Recent classifications have extended the range of LMs and have included various generalized lymphatic disorders under one umbrella.[4,5] Moreover, the arbitrary distinction of macrocystic and microcystic malformation on the size of cyst has been done away with. Cysts that can be successfully aspirated or sclerosed, resulting in the decrease in size of the lesion are considered significant.[6,7]

In the present series, all cases had multiple macrocysts, i.e., easily aspirate able, except the patient with breast LM, which was unilocular.

Clinically LMs are soft, compressible, nontender, transluminant, and lack bruit. However, these features only apply to macrocystic lesions, that too in the superficial head neck ones. Compressibility and transillumination can only be demonstrated in superficial head neck lesions. Thus for LMs at uncommon sites, diagnostic modalities are essential to establish the diagnosis. On ultrasound, it is multicystic with no flow on color Doppler study. CT scan and magnetic resonance imaging (MRI) reproduce the same features in difficult locations and help in determining the form, extent, and nature of the lesion. These cysts are usually filled with;

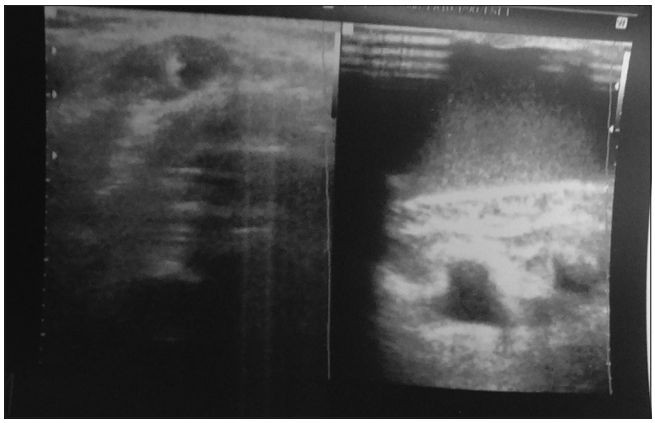

Figure 7: Ultrasound showing breast lesion resolved

straw-colored, serous, and less commonly, milky fluid if the cyst has prominent lymphatic communication, as seen in our case of Breast LM. The aspiration of serosanguinous fluid, with internal echoes on imaging, points to secondary infection or hemorrhage within the cyst.

Due to high morbidity and recurrence,[7] for head and neck LM, in many centers around the world, surgical interventions are reserved for cases that have a poor response to sclerotherapy. In contrast, clear cut guidelines for the management of LM at uncommon sites are not available, with the surgical intervention being the preferred modality.[8]

The known drawbacks of ILB are: requirement of multiple sessions, residual fibrotic soft-tissue mass, and incomplete resolution. In our center, all macrocystic lesions are subjected to ILB sclerotherapy as the first line of treatment. Surgical treatment of such lesions is reserved for three types of patients. First for patients who have poor response to sclerotherapy, second, who refuse sclerotherapy as a primary line of treatment and third, we offer surgical excision of small residual fibrotic mass for aesthetic reasons.

Approximately 80% of all LM's involve the cervicofacial region, followed by axillary region. In our review of literature, anterior chest wall lymphangioma in the pediatric age group is very rare and have been managed surgically.[9] This, we believe, is due to its rarity (<25 cases reported), leading to a lack of proper treatment protocol for its management. Our experience with ILB provides a simple nonsurgical alternative for the management of this rare entity. We could achieve complete resolution of the lesion in a single session ILB with no long-term recurrence.

Congenital LMs of the breast is extremely rare with <5 cases in the pediatric population,[10] and none of them had been reported in infants whereas both of our case are infants. Surgical management has been the preferred mode of treatment for such lesions till now. However, our management protocol provides a nonsurgical alternative, which will lead to a cosmetically superior result, especially for females though both cases in our series were male. This will ensure the preservation of normal breast tissue without leaving any scar after the procedure.

Similarly, LMs of substernal region and parotid are rare.[11] Treatment with ILB is simple and avoids multiple problems associated with surgical excisions such as sternotomy, the base of the neck, and intra-thoracic dissection for substernal LMs, facial nerve, parotid duct, and cervical plexuses injury in cases of parotid LM. In all these cases, we find that the absence of surgical excision provides a better aesthetic outcome for the child, which will be of great psychological significance when the child grows up.

Conclusive diagnosis of LM at atypical sites is a challenge; tissue diagnosis being the most exact is not possible in ILB therapy. However, ultrasound, Doppler study combined with clinical examination, aspiration of milky/serous/serosanguinous/straw-colored fluid and aided by CT/MRI in selective cases provides reasonably accurate diagnosis, as in our series. Hence, even in atypical sites histopathological confirmation of the diagnosis is only required in patients where clinical examination and radiological investigations are inadequate to reach a diagnosis. It has been our observation that most of the atypical lesions are relatively smaller in size as compared to head-and-neck lesions. Moreover, they contain multiple smaller cysts, unlike LM in the head-and-neck region, which have larger and fewer individual cysts.

Bleomycin is a cytotoxic anti-tumor agent, discovered by Umezawa in 1966. Endothelial mesenchymal transition has been advocated as one of the most important mechanisms of bleomycin-induced fibrosis in recent times, and its modulation can significantly decrease the incidence of pulmonary fibrosis, which one of the most dreaded complications of bleomycin.[12] Aqueous bleomycin is a mixture of A2 and B2, in which bleomycin A5 is also present (not >10%–15% of the mixture). The pharmacologic profile of all the molecules is almost the same, and hence, all show the same therapeutic effect.

Aqueous bleomycin, unlike lipid-based variant, is a cheap drug, easily available when compared with other sclerosing agents like OK-432. Since most of our patients come from low socioeconomic status bleomycin is also an economically viable alternative. Report of the intralesional aqueous solution of bleomycin is limited[13,14] though at our center we are using aqueous bleomycin with promising results.[15] The mode of action of belomycin in LM is the loss of secretory power caused by drug-induced inflammation on the endothelial lining rather than the killing of cells. Thus, we

believe aqueous bleomycin, which is economical and easily available, can be equally effective in dealing with LM if the principal of adequate contact time post aspiration is strictly adhered to.

Surgery has been the mainstay of treatment for atypical sites. However, our treatment protocol of post aspiration sclerotherapy of each individual cyst under ultrasound control provides a good nonsurgical treatment option for cystic hygroma at atypical sites. The good result in our series may have happened because of more intense inflammation on the cyst wall due to: complete aspiration of cystic fluid before putting bleomycin, the use of concentrated bleomycin solution (3 mg/ml), and postprocedural compression. Second, in the present series, the proposed interval between the two sessions was 6 months or more, which may be the optimum time for the desired action of drug, especially at atypical sites.

CONCLUSION

LM should be considered as a differential diagnosis of cystic lesion in the sites other than head and neck, especially in children and can be readily diagnosed by ultrasound. Aqueous ILB is a cost-effective alternative to surgery even at rare sites of cystic hygroma, which provide a better esthetic outcome, and avoids complications associated with surgery. Thus, we believe aqueous bleomycin, which is economical and easily available, can be equally effective in dealing with LM if the principal of adequate contact time post aspiration is strictly adhered to.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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