Original Article

Aqueous intralesional bleomycin sclerotherapy in lymphatic malformation: Our experience with children and adult

ABSTRACT

Objectives: Lymphatic malformations (LMs) are aberrant proliferation of sequestrated lymphatic vessels during early embryogenesis and do not communicate directly with the general lymphatic system. The absence of vascular flow is the hallmark of LMs and is usually symptomless apart from painless disfiguring mass with concerns regarding cosmesis.

Design: Sclerotherapy has gained prominence as a preferred treatment modality for macrocystic lesions. Here, we present our experience with use of aqueous bleomycin as intralesional sclerosing agent, an economical first-line treatment for macrocystic variant of LMs in children and adults. While bleomycin microsphere in oil has been commonly used in many previous studies, we have used aqueous bleomycin solution as the sclerosing modality which is easily available and economical.

Materials and Methods: Twenty-seven patients of macrocystic LM including adults and children underwent bleomycin sclerotherapy under ultrasonography guidance. Number of sessions, dose administered, and the response to therapy along with all side effects were noted.

Results: Sixteen patients received 3 or less sessions while rest needed 4–6 sessions of sclerotherapy for desired response. The response was excellent in 22 patients while 5 patients showed good response. Eleven patients developed minor side effects in form of fever, local infection, intracystic bleed, and local skin discoloration. Postsclerotherapy, surgery was performed in two patients.

Conclusion: The better response in the present study can be attributed to targeting of individual cysts in multiloculated lesion, ultrasound-guided aspiration of the cysts content before drug delivery, and postprocedure compression which increases the contact time between cyst wall and bleomycin reducing the chances of postprocedure seroma formation. Since the drug acts on the endothelial lining of the cyst, volume of the cyst is the major determinant in response. Aqueous bleomycin had comparable results with oil-based microsphere establishing it as an economical alternative treatment modality.

Keywords: Bleomycin, introduction, lymphatic malformation, sclerotherapy

INTRODUCTION

Vascular anomalies are a varied spectrum of disorders and have been broadly classified into vascular tumors and vascular malformations. Malformations are developmental anomalies due to inborn errors in vascular morphogenesis while vascular tumors are neoplastic lesions having a proliferative component.[1,2] Lymphatic malformations (LMs) are aberrant developmental anomaly of dysplastic sequestrated lymphatic vessels during early embryogenesis, lined by endothelial cells with a lymphatic phenotype. LMs were earlier classified

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as microcystic (cysts <1 cm in diameter) and macrocystic (cysts >1 cm diameter); however, new classifications have excluded this arbitrary criterion.[1,3] Although surgical treatment is the mainstay, sclerotherapy has gained prominence as a preferred modality of treatment, especially for macrocystic lesions. Intralesional bleomycin, an anti-cancer drug, was used as a sclerosing solution for the first time by Yura *et al*. who observed better resolution of symptoms in macrocystic LMs rather than microcystic type.[4] They also inferred that emulsified bleomycin solution was superior to aqueous solution. Cervical, facial, and axillary LMs are more commonly composed of macrocystic type. These areas are also cosmetically important.[5] Here, we present our experience with the use of aqueous bleomycin as an intralesional sclerosing agent and as an economical first-line treatment for macrocystic variant of LMs in children and adults.

MATERIALS AND METHODS

We retrospectively reviewed the data of all patients with LMs managed in our department from July 2009 to June 2014. All the patients of macrocystic LMs which were clinically diagnosed and supported by investigations and treated primarily by intralesional bleomycin were included in our study. Those patients with generalized lymphatic anomalies, microcystic and mixed lesions, associated other vascular anomalies, intra-thoracic, spinal, or retroperitoneal lesions, and patients with infection and lymphorrhea were excluded from the study. Patients who had prior surgery for LMs and having underlying pulmonary disease were also excluded from the study. Children and adults both were included in the study.

Data of all patients from electronic and hospital records including age, sex, weight, location of lesion, size, clinical history, special investigations, bleomycin dose, clinical response, side effects, and follow-up were recorded from the last 5 years. The patients were considered for intralesional injection of bleomycin under ultrasonography (USG) guidance after aspiration of clear lymphatic fluid only. Each patient received 1–6 doses of intralesional injection depending on the response at an interval of 4–6 weeks. Preceding next dose of sclerosing agent, each case was evaluated with USG for response. Any patient having no response after three successive doses was considered as nonresponder and further treatment was stopped. Such patients were counseled for undergoing alternative treatment in form of surgical intervention. Response was monitored clinically by measurement of the length and breadth of the clinically apparent lesion. Response was also measured on USG taking into consideration, two largest perpendicular dimensions on ultrasound, at the beginning of each dose. However, subjective parameters such as deformity correction and improvement in cosmesis were given preference while grading the response which was considered as excellent (total disappearance without indurations), good (>50% reduction), and poor (<50% decrease). The follow-up period ranged from 6 months to 5 years [Figures 1-3].

Procedure

All patients were admitted as in patients at the time of therapy in accordance with our hospital policy for any invasive procedure. While adults were treated on day care basis, children were observed overnight and discharged the next day. A baseline chest X-ray was done to rule out a preexisting lung pathologies such as pulmonary fibrosis, a known side effect of bleomycin. Procedure was performed under sedation or by laryngeal mask airway in children while in adults, it was done under sedation or local anesthesia after written consent. The lesion was identified by USG, and after skin puncture, the metallic stellate of the cannula was used to monitor the placement of the cannula in the cyst cavity under USG guidance. Once placement was confirmed, the metallic stellate was removed and the plastic cannula cover was left *in situ*. Clear lymphatic fluid was aspirated using a 20-gauge cannula. Every attempt was made to aspirate the cyst as much as possible so as to leave no or minimal fluid within the cyst. The aspirating cannula was left *in situ* and bleomycin solution was injected through the same cannula under USG guidance taking care not to dislodge the cannula from the cyst cavity. Drug delivery was ensured into the cyst cavity with USG.

Bleomycin solution was reconstituted so as to deliver 1 mg/ml of drug. For multilocular lesion, the same procedure was repeated for each individual cyst with total dose being divided in proportion to the size of the individual cysts [Figure 4].

The total cumulative injected dose of bleomycin aqueous solution did not exceed 5 mg/kg of body weight over all the sessions. Total dose of bleomycin per session was 0.5 mg/kg with a maximum dose of 10 units per session.[6,7] This was repeated monthly 1–6 times depending on the response.

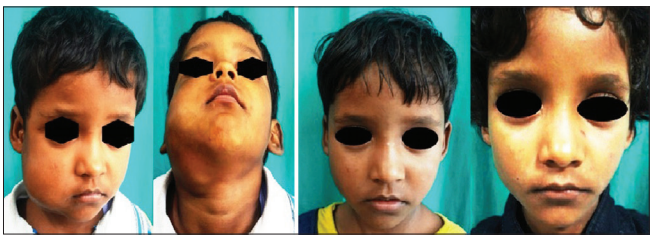

Figure 1: Long-term follow-up of cervicofacial lymphatic malformation

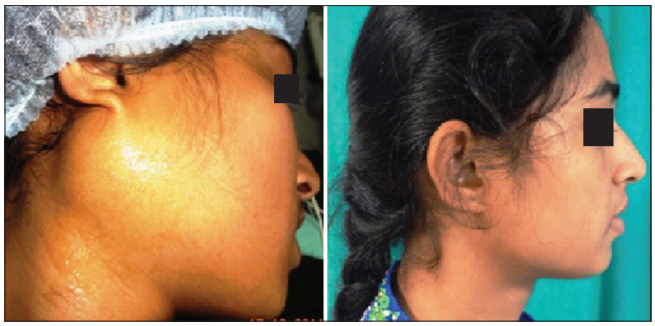

Figure 2: Complete resolution of parotid lymphatic malformation in adult

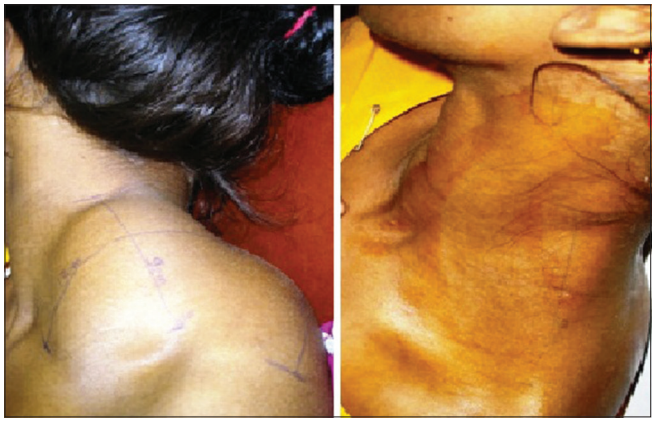

Figure 3: Good response in adult cervical lymphatic malformation

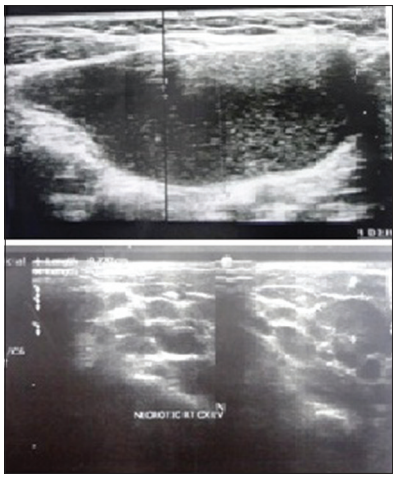

Figure 4: Ultrasonography can easily distinguish between micro- and macro-cystic lesions

Postprocedure, compression of the injection site was done for 6 h. Strict monitoring of the vitals was done during and 6 h postprocedure and patients, especially pediatric patients, were discharged after one night of observation. Postprocedure patients were observed for short-term complications such as pain, fever, and erythema at the local site. To rule out bleomycin-related pulmonary fibrosis, all patients underwent a repeat chest X-ray 6 months after the last bleomycin injection.

RESULTS

From July 2009 to June 2014, 27 patients with LMs were treated by intralesional aqueous bleomycin solution. Age ranged from 3 months to 52 years (median 14 years). Eighteen patients were <17 years (male:female = 11:7) while 9 patients were older than 17 years (male:female = 4:5). The neck region was most common site found in 15 patients followed by axilla and chest in 7 patients, face in 1 patient, and lumbar region in 1 patient. During USG, single significant macrocyst was found in 10 patients while 17 patients had more than one cysts (<3 cysts in 9 patients, 3–5 cyst in 6 patients, and >5 cysts in 2 patients) [Figures 2 and 3].

Out of 27 patients, 16 patients received 3 or <3 sessions while rest 11 needed 4–6 sessions of sclerotherapy for desired response. Interestingly, four patients only required single session for complete resolution of symptoms. The response was excellent in 22 patients while 5 patients showed good response. None of the patient had poor response. The initial volume (156 ± 50.01 ml) and final volume (24.67 ± 20.06) of lesions were compared using Wilcoxon signed-rank test. The $P < 0.005$ is highly statistically significant.

Out of 27 patients, 11 patients developed side effects in form of fever in 4; local infection in 2; transient increase in size in 1; intracystic bleed in 1; and local skin discoloration in 2 patients. One patient presented with local recurrence. This patient was lost in follow-up after three sessions of sclerotherapy and presented to us with swelling after 2 years. He was further managed by three more sessions of sclerotherapy. After completion of sclerotherapy, surgery was performed in two patients for cosmetic reasons.

DISCUSSION

LMs are common vascular malformation in infants and children and account for about 5% of all vascular malformations. Initially described by Wernher in 1843, it continues to be a challenging entity to this date.[8] The incidence is between 1 in 6000 and 1 in 16,000 live births with multifactorial genetics and they affect both sexes equally. LMs are seen at birth in 60% and in 80%–90% cases manifest by the age of 2 years.

All vascular malformations are caused due to errors of vascular development between 4th and 6th week of gestation.[9] Intrauterine LM detected on antenatal scans are associated with aneuploidy, multiple congenital anomalies, and fetal loss. Syndromes such as Turners, Noonan, and Trisomies are associated with intrauterine LM. On fetal scan, such LM can be detected in early pregnancy and generally contribute to

a bad obstetric history with increased chances of fetal loss. In contrast, intrauterine LM detected in late pregnancy is not associated with either aneuploidy or other syndromes. However, all patients having intrauterine LM should be assessed for other congenital anomalies. In such cases, intrauterine cyst size, sites, and invasion of surrounding tissue are important prognostic factors for fetal well-being.[10]

Recent classifications have extended the range of LMs and have included various generalized lymphatic disorders under one umbrella.[1] Moreover, the arbitrary distinction of macro- and micro-cystic malformation on the size of cyst has been done away with. Cysts which can be successfully aspirated or sclerosed resulting in the decrease in size of lesion are considered significant.[11]

The absence of vascular flow is the hallmark of LMs, apart from a painless disfiguring mass with concerns regarding cosmesis. Clinical symptoms usually depend on site of origin and sometimes may present with difficulties in breathing and/or swallowing or infection, which may be life-threatening. LMs are diagnosed clinically as a cystic mass which is brilliantly transilluminant, having a typical place of origin. However, this only applies to macrocystic lesions and transillumination can only be applied to superficial lesions. Diagnosis can be confirmed by USG, computerized tomography scan, or magnetic resonance imaging (MRI) [Figures 4 and 5]. MRI has additional advantage of demonstrating the infiltrating margin of lesion [Figure 5]. Although surgical excision has been the traditional modality of treatment, the presence of important structure in vicinity of LM and infiltration into surrounding tissue planes makes dissection difficult and also there is high recurrence rate, infection, and nerve damage (marginal division of mandibular nerve is most common).[7] In view of multiple problems with surgical excision, alternative therapeutic measures, i.e., sclerosing agents were developed with the hope that such technique would be equally effective.

Bleomycin is a cytotoxic antitumor agent, discovered by Umezawa in 1966. It is without bone marrow toxicity and not only does it have significant response in lymphomas, testicular tumors, and cutaneous squamous cell carcinoma but it has also become a common treatment option for a variety of benign cutaneous lesions such as warts and keloids. Bleomycin exhibits dual effect on human tissue including DNA degradation in under coiled strand regions and has specific sclerosing effect on vascular endothelium. Besides its cytotoxic effect, bleomycin also induces sclerosis.[12] The exact working mechanism in vascular malformations is poorly understood, but endothelial damage and fibrosis are supposed to play an important role.[13] 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.[14] Regression in LM is due to its direct action on the lymphatic endothelial lining producing an inflammatory response.[15] We feel that the desired effect of sclerosis is achieved by local action of bleomycin, and hence, administered drug dose should depend on the size of lesion rather than weight of the patient.

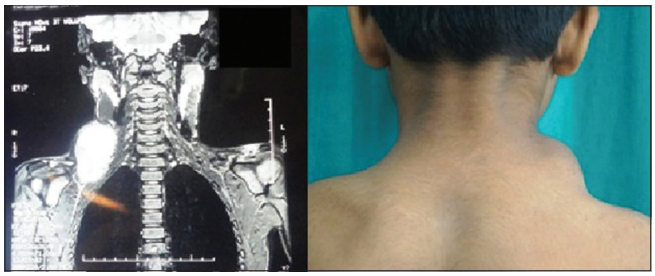

Figure 5: Magnetic resonance imaging can easily delineate deeper extension of the lesion

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.[12]

In previous studies, use of intralesional bleomycin has shown better results in macrocystic variety of LM.[16] Cervical, facial, and axillary lymphangiomas are more commonly composed of macrocystic type. These areas are also cosmetically important. Hence, bleomycin is a safe and effective intralesional agent for the treatment of macrocystic LM sand superficial LM lesions. For extensive macrocystic LMs involving contiguous anatomic areas and diffuse microcystic lesions involving deep tissues, bleomycin injection combined with resection is necessary.[17] Recent studies showed more than 50% cure rate (complete disappearance of the lesion) using intralesional bleomycin in cases of LM. In a systemic review of patients, good to excellent improvement was seen in 50%–100% of patients, with a mean of 84% of patients.[12] Baskin *et al.* in their study of 9 cases observed about 66.6% cases' lesion resolved completely after one injection and in two cases, they had to surgically excise the remnant tissue without any complication.[12,15]

In our study, more than 80% of the patients had excellent response with none of the patients having poor or no response [Figure 1]. Four of the patients had excellent resolution of the symptoms after a single dose of sclerotherapy. Our study has shown better response than many of the previous studies.

Before going into the mechanism of action of bleomycin as a drug, it is important to understand that intralesional bleomycin does not remove the lesion as in surgical management; however, bleomycin first reduces or eliminates the secretory function of the lesion and second decreases the size of the individual cysts. These actions not only reduce the size of the lesion but also prevent its recurrence, which we believe is the aim of the treatment. Thus, when grading the response to treatment, clinical improvement in the form of deformity correction and improvement of cosmesis were the major criterion. All patients at the end of treatment had some residual cysts. These cysts were either microcystic (not amenable to aspiration and sclerotherapy) or located in the deeper tissues or both, hence did not contribute to the esthetic deformity of the patient. We advise that postcompletion of the treatment protocol, all the patients especially in the pediatric age group, should be counseled about the residual lesion and the need for further sclerotherapy at a later stage in life. In our study, after a maximum follow-up of 5 years, only two patients have come back for the excision of the residual lesion. Both of these were superficial lesions where the residual fibrotic lesion had esthetic implications with the absence of any cystic space on USG.

The better response in the present study can be attributed to targeting of individual cysts in multiloculated lesion, ultrasound-guided aspiration of the cysts content before drug delivery, and postprocedure compression which increases the contact time between cyst wall and bleomycin reducing the chances of postprocedure seroma formation. Since the drug acts on the endothelial lining of the cyst, volume of the cyst is the major determinant in response. By aspirating the cyst, volume of the lesion is further reduced, and hence, higher concentration of the drug reaches the endothelial lining producing intense fibrosis and elimination of the endothelial secretory function. In contrast, other vascular scelrosants, such as polidocanol and ethanol, act intra- and peri-lesionally. This causes inflammatory reaction not only in the cyst but also in the surrounding normal tissue; hence, the chances of cosmetic deformity, i.e., cutaneous scarring and skin necrosis along with damage to vital structures such as facial nerve and parotid duct can be much more when compared with bleomycin sclerotherapy.[12]

Aqueous bleomycin, unlike lipid-based variant, is a cheap drug, easily available when compared with other sclerosing agents such as OK-432. Since most of our patients come from low socioeconomic status, bleomycin is also an economically viable alternative. Intralesional bleomycin microsphere in oil emulsion has reported good response because it is retained for longer period.[18,19] Report of intralesional aqueous solution of bleomycin is limited.[6] In our study, bleomycin aqueous solution has given good results. Superiority of emulsified solution was based on the notion that such solution is retained for a longer time in the cell and hence better neoplastic effect.[20] Unlike neoplastic lesions where cell death is essential for LM, loss of secretory power caused by drug-induced inflammation on the endothelial lining is sufficient for symptom resolution. 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 postaspiration is strictly adhered to.

LMs are nonneoplastic lesions. The aim of our management is not only to completely excise the lesion but also to reduce the size so that it is cosmetically acceptable with no chances of recurrence. Bleomycin sclerotherapy which eliminates the secretory function of the endothelium achieves our purpose. The disadvantage of major surgery, i.e., multiple scars over the face, potential damage to vital structures is eliminated. One of the drawbacks of bleomycin sclerotherapy is the potential pulmonary complications such as fibrosis and interstitial pneumonitis. However, these complications are seen in patients on intravenous bleomycin with cumulative dose >400 mg. The total dose in LM treatment is much lesser; hence, chances of complication are minimal.[16] Moreover, the side effects encountered in our study were transient and minimal with no long-term sequel. The lack of significant side effects as seen in our study makes aqueous bleomycin our preferred mode of sclerotherapy for macrocystic LMs in all age groups.

Surgery is reserved for the removal of residual fibrotic lesions for cosmetic purpose only as was done for two of our patients.

Inability to completely eradicate the lesion is one of the drawbacks of bleomycin sclerotherapy. This may lead to anxiety in the minds of the patients, especially parents of children regarding the chances of recurrence of the lesion on long-term follow-up. Moreover, chances of lymphangitis in the residual lesion are also a possibility. Hence, it is important to properly counsel the patients about the nature of the diseases process and the treatment done.

CONCLUSION

The classification of LM has changed considerably. Any cyst which can easily aspirated and sclerosed is a macrocyst. In our study, almost all patients had macrocystic variant of LMs with or without septations and showed good result

after intralesional aqueous bleomycin sclerotherapy. The desired effect of sclerosis occurred by the local action of bleomycin. It depends on the availability of the drug per unit of surface area of the lesion. Aqueous bleomycin solution has same efficacy as the oil-based variant and hence provides a cheaper and equally effective alternative. Bleomycin has minimal short term with virtually no long-term side effects such as pulmonary fibrosis. Patients and parents should be counseled about the residual lesion and proper follow-up should be emphasized. We infer that dose injected should depend on the size of the lesion rather than weight of the patient. Further studies with large cohorts are required to standardize the dose based on the size of the lesion if the LM can be aspirated completely, the concentration of the drug required per unit of surface area would be much less as compared to the lesions that are incompletely aspirated as the drug would get diluted in the hygroma fluid and less drug per unit of surface area would be available for the sclerosing effect.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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