Original Article

Bleomycin Sclerotherapy in Massive Macrocystic Lymphatic Malformation: Minimal Complications with Maximum Results

Ankur Bhatnagar, Zafar Neyaz, Brajesh Singh, Ashwani Mishra, Yusuf, Vijai Datta Upadyayaya, Basant Kumar

Department of Pediatric Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract

Introduction: Cystic lymphangioma (CL) is a multiloculated congenital malformation of the lymphatic system occurring in approximately 1 in 6,000–12,000 births, and it mostly presents at birth. The CL is of a variable size and it can be found at any age and in any part of the body. This study was carried out to observe the effect of intralesional aqueous bleomycin on giant CL presenting in adult and pediatric cases. **Materials and Methods:** This is an observational study conducted in the department of pediatric surgery and plastic surgery from January 2012 to January 2020. All the diagnosed cases of lymphangioma measuring more than 5 cm in size and managed during this period were reviewed. The cases who had lesions with a vascular component or who had any history of previous surgery or any form of treatment were excluded from the study. A total of 19 cases were included in the study. The primary mode of management of CL at the present center is intralesional bleomycin sclerotherapy (IBS). This is the standard protocol followed at our center to treat the cases with CL. Relevant demographic and clinical data of all the included patients were collected on a structured proforma, and data were analyzed. **Result:** Four cases had a favorable outcome in a single session, seven cases showed a favorable response after the second session, and three cases showed a favorable response after the third session. Two cases showed a partial response even after the fourth session and were considered nonresponders, one of whom was operated on and the other who was satisfied with a partial response and was not willing to undergo surgical excision. No major complications were observed in the present series. A few cases developed mild pain with or without fever, but none of them required hospitalization. **Conclusion:** Intralesional bleomycin sclerotherapy (IBS) is a safe, effective, and economical treatment option for the management of large cystic lymphangiomas and it avoids surgery-related complications.

Level of Study: IV evidence study

Type of Study: Retrospective observational study

Keywords: Bleomycin, lymphangiomas, sclerotherapy

Introduction

Lymphangiomas are common congenital benign lesions arising from a malformed lymphatic system. About 60% of the lesions appear at birth, and 80% are manifested within the first 2 years of life.[1] Lymphangiomas can be grossly divided into three categories: capillary, cavernous, and cystic. The cystic lymphangioma (CL) usually comprises a large cyst filled with protein-rich fluid, which can be unilocular or multilocular.[2] The CL amounts to 4% of all vascular malformations and is known for extensive infiltration in the surrounding tissues, thus making surgical excision difficult.[3] According to the size of the cysts in the lesion, CL is further classified into microcystic, macrocystic, and mixed subtypes.[4] The CL can be further subdivided on the basis of the liquid ingredient as a serous or chylous type, but its management is not affected by this subclassification.

The CL is a benign vascular malformation and it needs attention mainly because of aesthetic reasons and sometimes due to complications such as local inflammation,

Access this article online

Quick Response Code:

Website: www.jcasonline.com

DOI: 10.4103/JCAS.JCAS_108_20

Address for correspondence: Dr. Vijai Datta Upadhyaya, Department of Pediatric Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow Sanjay Gandhi Postgraduate Institute of Medical Sciences Lucknow, 226014, Uttar Pradesh, India.
E-mail: upadhyayavj@rediffmail.com

How to cite this article: Bhatnagar A, Neyaz Z, Singh B, Mishra A, Yusuf, Upadyayaya VD, *et al*. Bleomycin sclerotherapy in massive macrocystic lymphatic malformation: minimal complications with maximum results. J Cutan Aesthet Surg 2020;13:319-25.

infection, sinus formation, and hemorrhage.[5,6] It is usually congenital, where two-thirds of cases are found in the head and neck region, but sometimes it can be acquired.[7]

The management of head and neck CL is challenging because of its close association with the adjacent vital structures and poor demarcation of its boundaries. Treatment modalities available for CL in the current era are: surgery, sclerotherapy, and laser therapy, or a combination of these.[8] Surgery used to be the mainstay or even the only treatment choice and it still remains the first choice in the hands of many surgeons.[5] The traditional management of CL is surgery, with the aim of completing excision of the lesion without sacrificing vital structures. Due to the anatomical relationships in the head and neck, it can be cosmetically and/or functionally morbid. Second, these lesions have a tendency to recur, because complete excision is usually not possible due to widespread extension in the tissue plane. These factors lead to a search for the nonsurgical management for CL, such as sclerotherapy.[9,10] Numerous previous studies have shown good results in the management of giant CL, with a combination of sclerotherapy and surgery. This study was conducted to assess the effectiveness of intralesional bleomycin sclerotherapy (IBS) as the sole treatment modality for the management of giant CL.

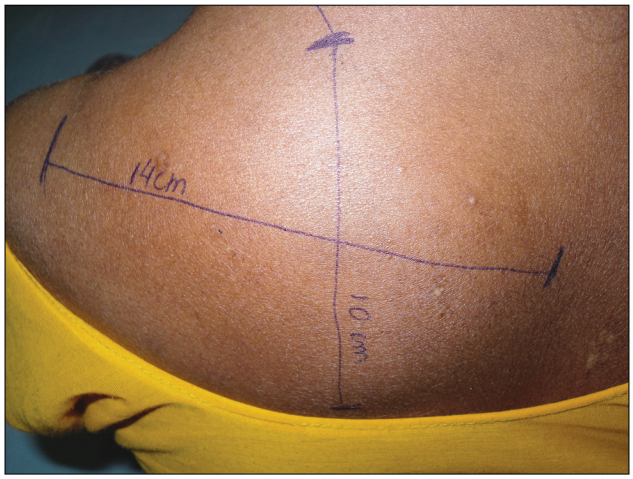

Figure 1: Showing large CL involving shoulder and scapular region

Materials and Methods

This retrospective observational study was carried out in the department of pediatric and plastic surgery in a tertiary care center of North India. All diagnosed cases of CL managed from January 2012 to January 2020 were reviewed. Diagnosis was based on history, clinical examination, ultrasound imaging, and nature of the aspirated fluid. Cases of CL having either a longitudinal or a transverse diameter more than 5 cm were included in the study. The cases with CL having a vascular component and with a history of any kind of intervention before presentation were excluded by using a color Doppler study of the lesion. In each case, the volume of the lesion was calculated as per the guidelines.[9] The CLs with intrabdominal or intrathoracic involvement were not included in the study.

A standard protocol is followed at our center to manage cases of CL and is mentioned next: a) In all cases, a chest X-ray is done before starting the treatment. If in any case a chest X-ray shows any unusual finding, then further workup of the patient is done with the consultation of a pulmonologist and the patient is advised an alternate option. b) Patients who are able to undertake a pulmonary

Table 1: Effect of intralesional bleomycin on lesion of different sizes

	Number of Cases	Average Number of IBS session				Outcome			Surgery Required	Complication
		1	2	3	4	F	P	NF		
Pediatric cases	6	3	2	1	0	6	0	0	0	Fever after ILS in two cases, redness over lesion site in three cases, and excessive pain in two cases
Adult cases	13	1	5	2	5	11	1	1	1*	Pain in two cases, fever in three cases, and redness over skin in one case
Male	7	-				7	1	0	*	
Female	12	-				11	0	1	1	
>10 cm in size	5	1	1	2	1	4	1	0	*	
5 to 10 cm in size	14	3	6	1	4	13	0	1	1	
Number of macro cysts three or less	8	3	3	2	0	8	0	0	0	
Number of macro cysts more than three	11	1	4	1	5	9	1	1	1*	
History of fever	3	-				2	0	1	1	
History of bleeding	1	-				0	0	1	1	

*Surgery indicated but patient was satisfied by the reduction in size

Fever: persistent fever more than 48 hours and requiring antipyretics

Pain: pain lasting for more than 24 hours and requiring analgesics

Redness over lesion: The temperature of the skin over the lesion site is raised and the skin is shiny, requiring antibiotics (oral)

function test are subjected to it (usually patients are adult patients) or if advised by the anesthesia team. c) Steps of the procedure[11]: i) The lesion is marked with a marking pen [Figure 1] followed by a ultra-sonography (USG) [Figure 2]. ii) The fluid is aspirated under ultrasound guidance [Figure 3C] in an operation theater to maintain proper asepsis {in the case of children the procedure is done under general anesthesia or sedation as per the requirement}. iii) A maximum of three to four cysts are tackled in one session if the cyst is multilocular (fluid is completely aspirated, making the targeted cyst completely collapsed; we usually target the cysts that are more than 1 cm in size). iv) The cannula is left *in situ* and bleomycin solution with a concentration of 3 IU of bleomycin/ml is injected into the cyst, ensuring that the total volume of the drug does not exceed the limit of 0.5 IU/Kg body weight. {we usually inject a small amount of reconstituted solution of bleomycin into the vicinity of cysts that are not amenable to aspiration, that is, cysts measuring less than 1 cm in size} v) The site of the lesion is compressed with a bandage wherever it is possible, to minimize the bleeding and to increase the contact of the drug with the endothelial lining of the cyst for a better result. The patients are followed up with USG to observe the effect in size and especially the volume of the lesion at 8 to 12 weeks. (vi) The second session is conducted if required at the first follow-up and subsequently at an interval of 3 months for a maximum of 4 sessions or if the lesion is found to be not amenable for sclerotherapy on ultrasound scanning of the lesion. vii) The response is classified as

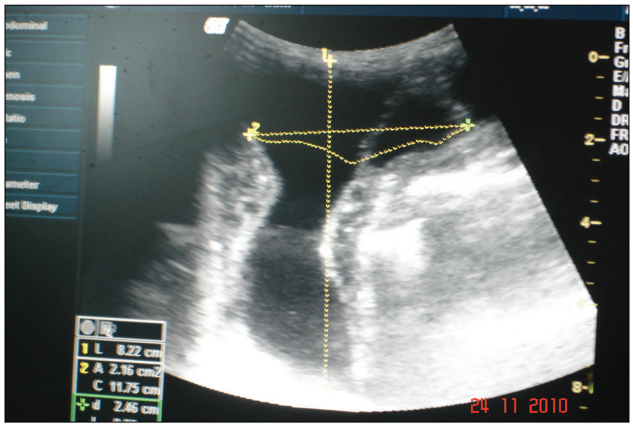

Figure 2: Ultrasound of the lesion in [Figure 1]

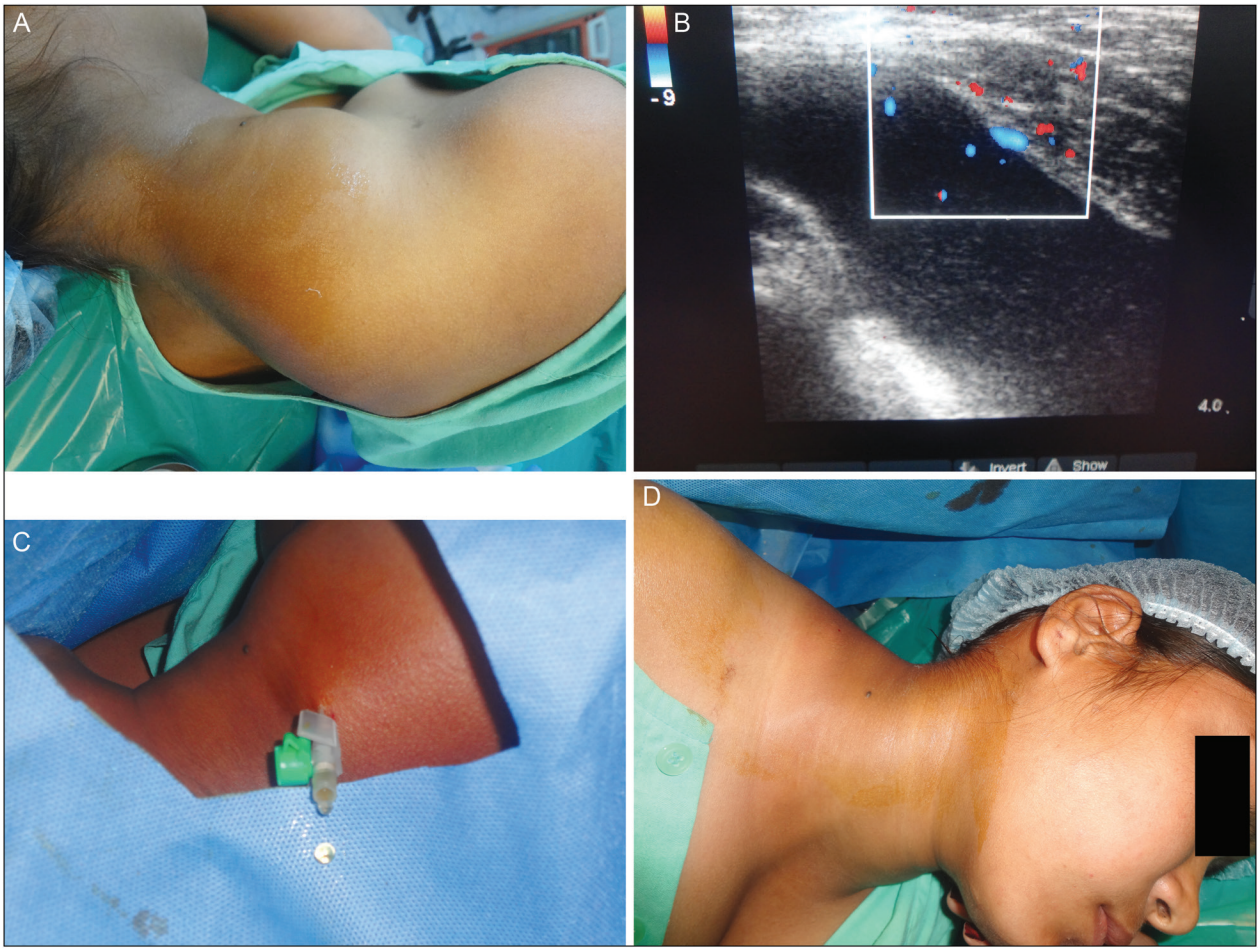

Figure 3: A: CL Showing right root of neck. B: Ultrasound of lesion in right root of neck. C: Showing aspiration of the content of the CL. Showing right root of neck. D: Response after single session

favorable (more than a 90% reduction in volume of the lesion), partial (a reduction of 10–90% of the lesion), or unfavorable (less than a 10% reduction of the lesion).[12] The volume is assessed by a Doppler ultrasound at the time of presentation and follow-up. (vii) Follow-up is done at 3, 6, and 9 months for the first year and 6 monthly for the next 2 years.

Results

A total of 21 cases of diagnosed CL with outer diameters measuring more than 5cm were managed during the study period. Two of these cases had a history of previous intervention, hence they are not included in the present study. Out of the 19 cases included in the study, 6 were pediatrics and the rest were adults. In 14 cases, the longest outer diameter was between 5cm and 10cm; in others, the longest surface diameter of the lesion measured more than 10cm [Table 1].

Four cases had a favorable outcome in a single session [Figure 3A to D], seven cases showed a favorable response after the second session, and three cases each after the third [Figure 4A to E] and fourth session showed a favorable response. Two cases showed a partial response even after the fourth session and were considered nonresponders, one of whom was operated on and the other who was satisfied with a partial response and was not willing to undergo surgical excision [Figure 5A to C]. No major complications were observed in the present series. A few cases developed mild pain with or without fever, but none of them required hospitalization.

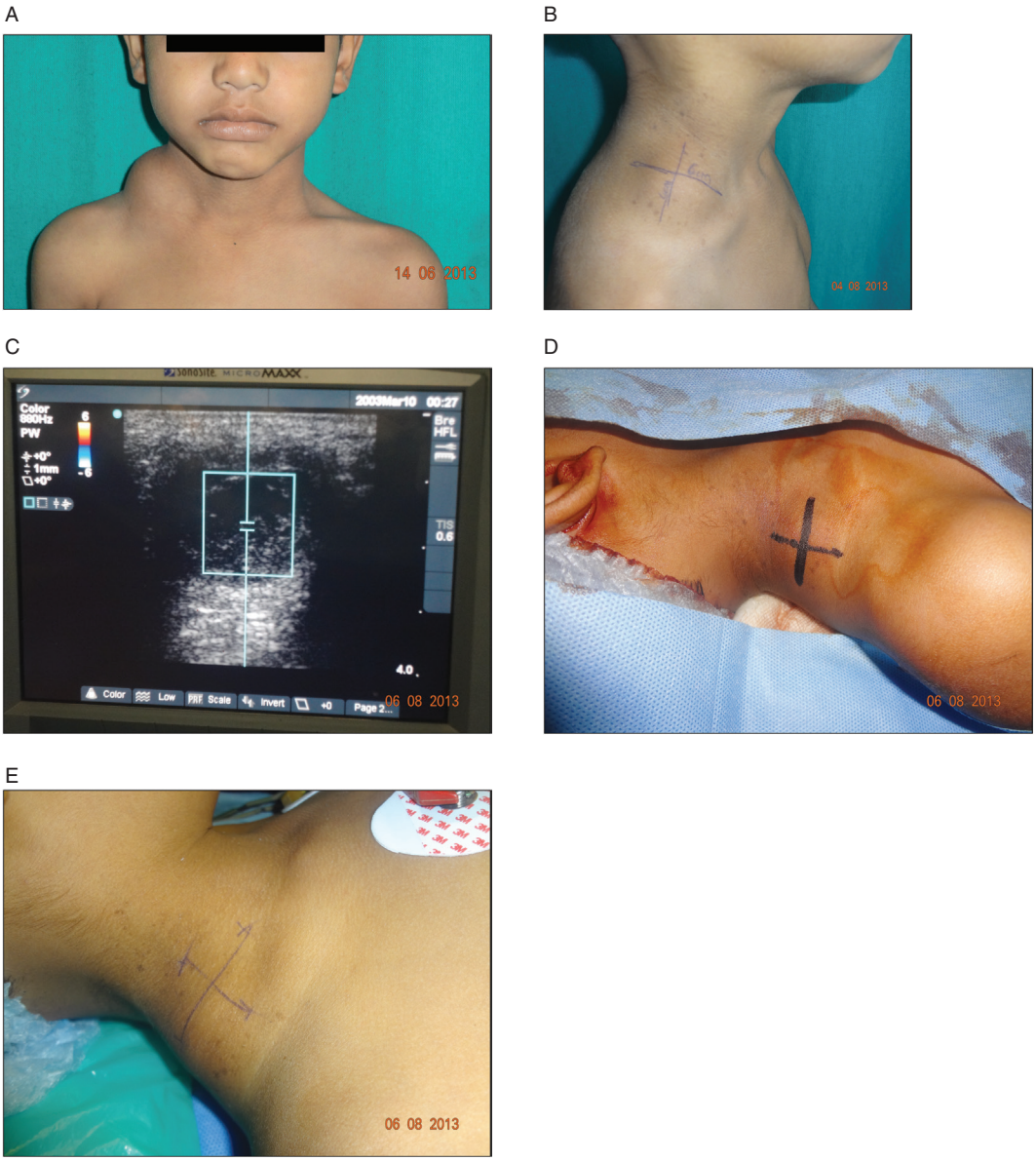

Figure 4: A: Large cystic lesion at right neck. B: Right root of neck lesion after one session of IBS. C: Ultrasound of lesion in [Figure 8]. D: Lesion in [Figure 7] after second session. E: Lesion in [Figure 7] after third session (resolved)

Statistical analysis

Data were entered in excel and scrutinized errors. For continuous parameters such as age, a median with min/max was calculated. Further, in case of a categorical value frequency, a percentage was calculated by using RStudio software. Inc., Boston, MA URL http://www.rstudio.com/.

Discussion

Lymphangiomas are believed to arise from an embryological defect that consists of an abnormal connection from the jugular sac to the peripheral lymphatic system.[13] The most common site of occurrence of CL is the posterior triangle of the neck (75%) and axilla (20%), but it can manifest anywhere in the body; however, the CL is most commonly seen in cervico-facial regions (especially in posterior cervical triangle), axilla, mediastenum, groin, and oral cavity.[14] The incidence of lymphatic malformation is 2-8%. The CLs can be found at any age of life but around 58% are seen at birth and almost 90% are diagnosed before the age of 2 years.

Lymphangiomas are usually classified as capillary lymphangioma, cavernous lymphangioma, and cystic lymphangioma. Cystic lymphangioma is also known as cystic hygroma.[15] Lymphangiomas can also be classified on the basis of the sizes of the cysts as microcystic, macrocystic, and mixed lymphangiomas. The size of the cyst in microcystic lymphangiomas is less than 2 cm; however, in macrocystic lymphangiomas, the size of the cyst is more than 2 cm, and in mixed lymphangiomas, the cysts are of a variable size.[16] The CL is more common as compared with other types of lymphangiomas, and it is usually composed of single or multiple macrocystic lesions.

The CLs appear as a soft, transilluminant, compressible, and nontender mass. Hence, the diagnosis of CL is usually clinical, based on history and a physical examination that can be confirmed on USG of the swelling. The CL, which involves deeper structures, needs computed tomography scans and magnetic resonance imaging for better surgical management.

On histology, CLs are characterized by a single-layer endothelium containing: clear watery (lymph) or serous or chylous fluid; they consist of multiple dilated locules sacs, which are supported by connective tissue stroma, interspaced with lymphocyte follicle cells and occasionally germinal centers.[5] Grossly larger cysts are usually located in the periphery, whereas smaller ones occupy a central and/or deeper part in typical lesions of CL. These smaller cysts usually infiltrate into the neighboring structures[17] and make the surgical excision difficult.

Indication treatments for CL are: disfigurement, large size, rupture, hemorrhages in the lesion, and recurrent infections.[18] In spite of multiple reports of nonsurgical methods for the management of CL, sclerotherapy is still the gold standard and most preferred treatment for CL; surgical excision is especially used for giant CL.[16-18] The drawbacks of the surgical management of CL are: i) quite a large number of CL involves tissues such as the cheek, lip, and tongue where complete surgical excision is not acceptable cosmetically; (ii) these lesions are poorly demarcated and, hence, complete excision is difficult; (iii)

Figure 5: A: Massive lesion in the axilla. B: Aspiration of the content from the lesion. C: Axillary lesion after fourth session

the involvement of the vital structures by diffuse extension; and (iv) complications such as large tissue defects are seen in around 3.1% cases, heavy bleeding occurs in around 1.6% cases, and infection may occur in around 2.5% cases.[5] Intralesional sclerotherapy, in contrast, preserves the salivary gland and the surrounding vital structures while selectively targeting the CL, hence sclerotherapy can be considered a viable option and developed as an alternate mode of treatment for CL. Many agents were used as sclerosing agents, but the most popular and effective agents are OK-432[19-21] and bleomycin.[22,23] We used IBS as a primary modality of treatment, even in the cases of giant CL involving the head and neck area, base of the neck, shoulder, and axilla. The reasons for using bleomycin in the present study were: i) easy availability of the drug in the Indian subcontinent, ii) its low cost, iii) being very effective[24-27] and almost comparable to OK-432,[28] and iv) negligible side effect—the only noticeable side effect is pulmonary fibrosis, which is not documented with the amount of the drug used in IBS. The local side effects mentioned in the literature are excessive pain, redness of the overlying surface, and fever, which usually subside on their own. In this study, none of the patients had noticeable local side effects, mainly because proper asepsis was maintained during the procedure and the drug was delivered in the lesion under ultrasound to avoid any spillage in the normal tissue.

Although the intralesional sclerotherapy with bleomycin had gained acceptability for the management of head and neck macrocystic lymphatic malformation, its role in the management of giant lymphangioma was not clear. Our study has shown that bleomycin can be used as a safe and effective sclerosing agent for treating a CL of any size. It not only treats the lesion but also preserves the function of the involved tissue, with adequate cosmetic results.

Limitation of study

This study, although a novel therapeutic intervention, has some limitations. The small sample size, lack of comparison with other treatment modalities, and the absence of randomization are the major shortcomings of this study.

Conclusion

Based on our experience of intralesional bleomycin, which is the first-line treatment modality for head and neck CL, we believe that this should also be the first-line treatment even for giant CL. Bleomycin sclerotherapy delivered under ultrasound guidance with direct puncture of the individual cysts can provide a safe, easy, and reproducible treatment modality for the management of this rare entity though a larger study and trial is required for a definitive conclusion.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form/forms, 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. McGill TJ, Mulliken JB. Vascular anomalies of the head and neck. In: Cumming CW, Friedrickson JM, Harker LA. editors. Text book of Otolaryngology-Head and Neck Surgery. 2nd ed. Washington, DC: Mosby Publishers; 1993. p. 333-6.
2. Christopher DM. Diagnostic histopathology of tumors. In: St. Louis editor. Vascular tumors. 3rd ed. Amsterdam, The Netherlands: Elsevier Publishers; 2007. p. 67-8.
3. Puri S. Cystic lymphangioma of parotid in adult - A rare entity. Indian J Case Reports 2018;4:239-41.
4. Giguère CM, Bauman NM, Smith RJ. New treatment options for lymphangioma in infants and children. Ann Otol Rhinol Laryngol 2002;111:1066-75.
5. Zhou Q, Zheng JW, Mai HM, Luo QF, Fan XD, Su LX, *et al*. Treatment guidelines of lymphatic malformations of the head and neck. Oral Oncol 2011;47:1105-9.
6. Greinwald Jr JH, Burke DK, Sato Y, Pous RI, Kimura K, Bauman, *et al*. Treatment of lymphangiomas in children: An update of Picibanil (OK-432) sclerotherapy. Arch Otolaryngol Head Neck Surg 1999;121:381-7.
7. Brock ME, Smith RJ, Parey SE, Mobley DL. Lymphangioma. An otolaryngologic perspective. Int J Pediatr Otorhinolaryngol 1987;14:133-40.
8. Zheng JW, Zhou Q, Yang XJ, Wang YA, Fan XD, Zhou GY, *et al*. Treatment guideline for hemangiomas and vascular malformations of the head and neck. Head Neck 2010;32:1088-98.
9. Xu DP, Zhai QK, Cheng C, Gong H, Wang HW, Wang XK. Appraisal of efficacy and safety of intralesional injection of high concentration of bleomycin A5 for treatment of huge macrocystic lymphatic malformations in cervical region. J Craniofac Surg 2014;25:1707-9.
10. Acevedo JL, Shah RK, Brietzke SE. Nonsurgical therapies for lymphangiomas: A systematic review. Otolaryngol Head Neck Surg 2008;138:418-24.
11. Upadhyaya VD, Bhatnagar A, Kumar B, Neyaz Z, Kishore JS, Sthapak E. Is multiple session of intralesional bleomycin mandatory for complete resolution of macrocystic lymphatic malformation? Indian J Plast Surg 2018;51:60-5.
12. Hugo de Oliveira Olímpio, Joaquim Bustorff-Silva, Antonio Gonçalves de Oliveira Filho, Kleber Cursino de Araujo. Cross-sectional study comparing different therapeutic modalities for cystic lymphangiomas in children. Clinics (Sao Paulo) 2014;69:505-8.
13. Leo H, Cheng H, Wells FC. A multidisciplinary approach to recurrent cervicothoracic cystic hygroma in an adult. Br J Oral Maxillofac Surg 2004;42:66-8.
14. Mirza B, Ijaz L, Saleem M, Sharif M, Sheikh A. Cystic hygroma: An overview. J Cutan Aesthet Surg 2010;3:139-44.

15. Fonkalsrud EW. Lymphatic disorders. In: Grosfeld Jay L, O'Neill JA, Fonkalsrud EW, Coran AG, editors. Text book of pediatric surgery. 6th ed. Washington, DC: Mosby Publishers; 2006. p. 2137-46.
16. Kumar N, Kohli M, Pandey S, Tulsi SP. Cystic hygroma. Natl J Maxillofac Surg 2010;1:81-5.
17. Jaiswal AA, Garg AK, Ravindranath M, Sarkar J, Mohanty MK. A huge congenital cervical lymphangioma – Case report with review of literature. Egypt J Ear Nose Throat Allied Sci 2015;16: 283-90.
18. Grasso DL, Pelizzo G, Zocconi E, Schleef J. Lymphangiomas of the head and neck in children. Acta Otorhinolaryngol Ital 2008;28:17-20.
19. Ogita S, Tsuto T, Nakamura K, Deguchi E, Tokiwa K, Iwai N. OK-432 therapy for lymphangioma in children: Why and how does it work? J Pediatr Surg 1996;31:477-80.
20. Aluffi Valletti P, Brucoli M, Boffano P, Benech A, Toso A, Dell'Era V, *et al*. A single-center experience in the management of head and neck lymphangiomas. Oral Maxillofac Surg 2020;24:109-15.
21. Efe Nihal, Altas Enver, Mazlumoglu MuhammetRecai, Aktan Bulent, Ucuncu Harun, Eren Suat, *et al*. Excellent result with the use of single-dose OK-432 in cervical macrocystic lymphangioma. J Craniofac Surg 2016;27:1802-3.
22. Yura J, Hashimoto T, Tsuruga N, Shibata K. Bleomycin treatment for cystic hygroma in children. Nihon Geka Hokan 1977;46:607-14.
23. Sonmez Kaan, Karabulut Ramazan, Turkyilmaz Zafer. Macrocystic lymphangioma in children treated by sclerotherapy with bleomycin. J Craniofac Surg 2020;31:250-1.
24. Ardıçlı B, Karnak İ, Çiftçi AÖ, Tanyel FC, Şenocak ME. Sclerotherapy with bleomycin versus surgical excision for extracervical cystic lymphatic malformations in children. Surg Today 2016;46:97-101.
25. Kumar V, Kumar P, Pandey A, Gupta DK, Shukla RC, Sharma SP, *et al*. Intralesional bleomycin in lymphangioma: An effective and safe non-operative modality of treatment. J Cutan Aesthet Surg 2012;5:133-6.
26. Abdur-Rahman LO, Awolaran O, Nasir AA, Bamigbola KT, Abdulraheem NT, Oyinloye AO, *et al*. Efficacy of bleomycin for non-operative treatment of cervical lymphangioma in University of Ilorin Teaching Hospital, Nigeria. J Med Trop 2017;19:93-7.
27. Parashar G, Shankar G, Sahadev R, Santhanakrishnan R. Intralesional sclerotherapy with bleomycin in lymphatic malformation of tongue an institutional experience and outcomes. J Indian Assoc Pediatr Surg 2020;25:80-4.
28. Olímpio Hde O, Bustorff-Silva J, Oliveira Filho AG, Araujo KC. Cross-sectional study comparing different therapeutic modalities for cystic lymphangiomas in children. Clinics (Sao Paulo) 2014;69:505-8.