Spontaneously Resolved Macrocytic Lymphatic Malformations: Predictive Variables and Outcomes

Les malformations lymphatiques macrokystiques spontanément résolutives : variables prédictives et résultats cliniques

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Abstract

Introduction: Lymphatic malformations are benign, low-flow vascular malformations that typically present at or near birth. Due to morbidity associated with operative treatment, nonoperative treatment with injection of sclerosant has become the mainstay of therapy. Over the past 15 years, several patients at our centre with macrocystic (>2 cm cyst size) lymphatic malformations have seen their lesions resolve spontaneously while awaiting treatment. In this study, we review features of these patients that may contribute to spontaneous resolution. **Method:** A retrospective chart review was conducted from our Vascular Anomalies Clinic database (1999-2014) of all macrocystic lymphatic malformations; characteristics of patients with spontaneous resolution were reviewed. **Results:** Of 61 patients with macrocystic lymphatic malformations, 7 cases (11.5%; 4 females, 3 males) resolved spontaneously. Median age at malformation appearance was 2 years (range: 0-6.5 years), with median age at resolution of 4 years (range: 10 months-7 years). Median time from appearance to resolution was 24 months (range: 3-43 months), with a median follow-up time of 4 years (range: 1-15 years). All but 1 case was associated with local or upper respiratory tract infection antecedent to resolution. Six of the 7 lesions were located in the neck. **Conclusion:** Among the cases reviewed, there was a common theme of upper respiratory tract or local infection antecedent to spontaneous lesion resolution. Compared to the literature, our proportion of malformations presenting after birth and the proportion of malformations presenting in the neck region were higher than those of other series. Although side effects associated with treatment are generally mild and/or rare, risks related to sclerotherapy and the accompanying requirement for general anesthesia in pediatric populations nevertheless exist. As the median time from lesion appearance to resolution was 24 months, it may be reasonable to observe these malformations for up to 24 months before proceeding with treatment if the lesion does not impair function and disfigurement is not considerable, particularly if the lesion presents after birth and/or is located in the neck region.

Résumé

Historique : Les malformations lymphatiques sont des malformations vasculaires bénignes à faible débit généralement présentes à la naissance ou peu après. Étant donné la morbidité associée à l'opération, le traitement non opératoire par injection de sclérosant est devenu la norme. Depuis 15 ans, plusieurs patients ayant une malformation lymphatique macrokystique (kyste de plus de 2 cm) qui ont été suivis au centre des chercheurs ont vu leurs lésions disparaître d'elles-mêmes pendant l'attente d'un

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traitement. Dans la présente étude, les chercheurs analysent les caractéristiques de ces patients qui sont susceptibles de contribuer à cette résolution spontanée. **Méthodologie** : Les chercheurs ont réalisé une analyse rétrospective des dossiers de la base de données de la clinique des anomalies vasculaires (1999-2014) afin d'en extraire toutes les malformations lymphatiques macrokystiques et ils ont examiné les caractéristiques des patients chez qui la malformation s'était résolue spontanément. **Résultats** : Chez les 61 patients présentant une malformation lymphatique macrokystique, sept cas se sont résolus spontanément (11,5 %; quatre filles, trois garçons). Ces derniers avaient un âge médian de deux ans (plage de 0 à 6,5 ans) à l'apparition de la malformation, et un âge médian de quatre ans (plage de dix mois à sept ans) à la résolution. La période médiane entre l'apparition et la résolution s'élevait à 24 mois (plage de trois à 43 mois), et la durée de suivi médian, à quatre ans (plage de un à 15 ans). Tous les cas, sauf un, s'associaient à une infection locale ou à une infection des voies respiratoires supérieures qui avait précédé la résolution. Six des sept lésions se situaient au niveau du cou. **Conclusion** : Parmi les cas étudiés, on constatait la présence d'une infection des voies respiratoires supérieures ou d'une infection locale avant la résolution spontanée de la lésion. Par rapport aux données contenues dans les publications, la proportion de malformations observées après la naissance et de malformations présentes dans la région du cou était plus élevée que dans les autres études. Même si les effets secondaires associés au traitement sont généralement légers ou rares, les populations pédiatriques courent tout de même des risques liés à la sclérothérapie et à l'anesthésie générale connexe. Puisqu'une période médiane de 24 mois s'écoulait entre l'apparition de la lésion et sa résolution, il peut être raisonnable d'observer ces malformations jusqu'à 24 mois avant le traitement si la lésion ne nuit pas à la fonction et ne défigure pas l'enfant de manière considérablement, particulièrement si elle se forme après la naissance ou si elle est située dans la région du cou.

Keywords

macrocytic lymphatic malformations, treatment

Introduction

Lymphatic malformations are a subset of vascular malformations involving anomalies of lymphatic vessels that are thought to arise in utero.¹ The majority of these slow-flow malformations are clinically appreciable at birth, however, a proportion do not present until later in life. They are most frequently subclassified by intralesional cyst size, with a floor of 2 cm generally being used to differentiate microcystic and macrocystic malformations.² In the past, these have been referred to as lymphangiomas and cystic hygromas,^{1,2} but for the purposes of this study, we will use the International Society for the Study of Vascular Anomalies (ISSVA) nomenclature. Mixed lesions with both microcystic and macrocystic components are not uncommon.

Intralesional injection sclerotherapy has become the mainstay of treatment for macrocystic lymphatic malformations (MacLMs), with a variety of sclerosant agents including OK-432 (Picibanil), bleomycin, ethanol, sodium tetradecyl sulphate, and doxycycline used.² OK-432 is a lyophilized mixture of group A *Streptococcus pyogenes*³ first proposed in 1987 as a sclerosant agent for treatment of MacLMs that has since gained considerable popularity and has been the sclerosant agent of choice for these lesions at our centre for over 15 years. Multiple studies have established the safety and efficacy of OK-432 sclerotherapy,^{4,5} with a recent multicentre review finding excellent outcomes in 88% of MacLMs treated with OK-432.⁶ Surgical excision is a less common treatment modality due to frequent anatomical obstacles resulting in subtotal resection or morbidity associated with damage to surrounding structures.^{7,8}

A few retrospective studies have investigated subsets of patients with MacLMs that have seen spontaneous clinical resolution of their malformations without receiving treatment.⁹⁻¹¹ However, the retrospective nature and small sample sizes of

these studies mean that few definitive conclusions have been drawn. Over the past 15 years, we have noticed a similar subset of patients at our centre with spontaneous resolution of their MacLMs. Although this case series is also retrospective in nature, this study aims to better characterize patients with spontaneous resolution at our centre, elucidate any factors that may contribute to spontaneous resolution, and compare the results of our review with those from other centres.

Methods

We retrospectively reviewed cases of patients presenting with MacLMs to the Vascular Anomalies Clinic (VAC) at BC Children's Hospital between 1999 and 2014, inclusive. Approval for this study was granted by the University of British Columbia Children's and Women's research ethics board (#H14-01564).

Inclusion criteria for this case series were patients seen at the VAC at BC Children's Hospital between 1999 and 2014, who were diagnosed with MacLMs, and who experienced spontaneous clinical resolution of their MacLM without receiving treatment. Study patients were identified through a review of the BC Children's Hospital VAC database, and the identified cases were compared to the total number of MacLMs in the database to determine a run rate. Data collected from patient records included demographics, patient history, clinical presentation (including anatomical location of malformations), radiologic images and characteristics, photographs, and clinical outcome.

Results

Of 61 patients presenting with MacLMs from 1999 to 2014, we identified 7 (11.4%) cases where patients experienced clinical

Table 1. Summary of Patient Variables and Outcomes.

Study ID	Gender	Age at Appearance, Years	Age at Disappearance, Years	Time to Resolution, Months	Follow-Up, Years	Antecedent Event	Location	Planned Treatment
1	F	1	1	10	1	Yes, local infection	Right neck, posterior	OK-432
2	F	0.5	4	43	4	No	Right cheek/mandibular angle	OK-432
3	M	5	7	25	8	Yes, URTI	Left neck	OK-432
4	M	3	5	24	15	Yes, <i>Streptococcus</i> pharyngitis	Right flank	Not OK-432 amenable
5	F	2	2	3	1	Yes, URTI	Right neck	None
6	M	6.5	7.5	13	4	Yes, URTI	Right neck, posterior	None
7	F	0	2	24	2	Yes, suspected <i>Streptococcus</i> infection	Left neck	OK-432

Abbreviation: URTI, upper respiratory tract infection.

recurrence-free resolution of their lymphatic malformation without receiving treatment. Table 1 summarizes key characteristics of the cases included in this series.

Four female and 3 male patients were identified with a median age at malformation presentation of 2 years (range: birth to 6.5 years). Two malformations were identified at birth, however, one of these cases was only noted on delivery and was not formally diagnosed until it recurred at a later age. In all cases, diagnosis of MacLM was confirmed by ultrasound, computed tomography, or magnetic resonance imaging. The median age at resolution was 4 years (range: 10 months-7 years), with median time from appearance to resolution of the malformation being 24 months (range: 3-43 months). Median follow-up time was 4 years (range 1-15 years). All but 1 case was associated with an antecedent local or upper respiratory tract infection. Six of the 7 malformations were located in the neck region, with the remaining malformation presenting in the flank region.

Representative Case

Case 6

Case 6 involves a patient who presented with 2 distinct episodes where the malformation was clinically appreciable in the same location but resolved spontaneously each time.

History

A healthy Caucasian boy initially presented to his community pediatrician at the age of 6.5 years with a lesion in the right neck that appeared over the course of a day. His parents did not note any associated trauma and he appeared otherwise well. He was referred to otolaryngology at BC Children's Hospital, who then sent him for an ultrasound and redirected his referral to the Plastic Surgery clinic. The lesion remained quiescent for 12 months. Approximately 1 year later at 7.5 years of age, the lesion developed an overlying erythematous rash. An ultrasound was performed and, upon review, was felt to be

consistent with a MacLM. His referral was directed to Plastic Surgery, but 4 weeks after recurrence the malformation disappeared, concurrent with an episode of sore throat and fever.

Physical Examination

The lesion was located in the right posterior triangle of the neck, superior to the clavicle and posterior to the sternocleidomastoid. It was soft and measured approximately 3 × 2 cm. No skin changes were noted at the initial presentation, but a slightly erythematous overlying rash was noted at the second presentation.

Radiological Findings

An ultrasound done identified a 3 × 2 × 1.8 cm macrocystic lesion with septations in the right posterior neck, 1 cm above the clavicle and 0.5 cm posterior to the sternocleidomastoid.

Clinical Course

This patient has since remained recurrence free at 3-year follow-up. Figure 1 represents the patient's clinical photographs and ultrasound findings.

Discussion

In this study, we have reviewed the clinical and radiographic history of 7 patients at our centre who have experienced spontaneous resolution of their MacLMs. From a total of 61 cases of MacLMs seen, we found 7 cases that met our inclusion criteria for spontaneous resolution for a 11.4% run rate of spontaneous resolution. Although this is not a large proportion, it is nevertheless a notable number of cases.

Temporally, there was a large variance in time from presentation to resolution in our series, with a range of 3 to 43 months. Similarly, there was no obvious pattern in age at time of presentation. However, only 2 (29%) patients in our

Figure 1. Six and a half-year-old male with a right neck lymphatic malformation and ultrasound (top), following spontaneous resolution (bottom).

series had a clinically appreciable lesion at birth, and only 1 of these was formally diagnosed with a MacLM at birth. Four (57%) cases had initial presentation after 2 years of age. This is in contrast to the background literature, where previous studies have found that approximately 50% of all MacLMs are appreciable at birth and 90% present before 2 years of age.^{12,13}

Of 7 cases of spontaneous resolution considered in this study, 6 (86%) cases presented with malformations in the neck region. This is higher than the proportion of all MacLMs occurring in the neck region as indicated by the background literature,^{14,15} which varies from 45% to 62% at most.¹⁶ All but 1 case in this series had history of an upper respiratory tract infection or local infection of the malformation event antecedent to spontaneous resolution, with 1 patient having group A streptococcal pharyngitis confirmed on throat swab.

OK-432 consists of a lyophilized group A *S pyogenes* preparation which leads to speculation that finding spontaneously resolving malformations tend to be located in the neck and temporally associated with upper respiratory tract infection may be the result of a similar process from spontaneous group A *Streptococcus* infection. However, evidence is insufficient in this study to draw a strong conclusion as we do not have culture results for all patients.

All 7 cases involved singular/isolated lymphatic malformations, which did not have significant functional impact for the

patients. The above findings are fairly consistent with the previous literature, including a similar case series by Perkins et al.⁹

This study is limited by the small sample size and retrospective nature of this review. In the future, it would be interesting to undertake comparison with nonspontaneously resolving MacLMs or a multicentre study or prospective study to better characterize this population of patients.

Conclusion

Among the cases reviewed here, there was a common theme of upper respiratory tract or local infection antecedent to spontaneous resolution of MacLMs. Compared to the literature, the proportion of malformations presenting after birth and the proportion of malformations presenting in the neck region were higher than respective proportions for all MacLMs. This suggests that malformations that present after birth and that are located in the neck region may be more likely to resolve spontaneously. Although side effects associated with treatment are generally mild and/or rare, risks related to injection sclerotherapy and the accompanying requirement for general anesthesia in pediatric populations nevertheless exist.

As the median time from lesion appearance to resolution was 24 months, it may be reasonable to observe these malformations for up to 24 months before proceeding with treatment if the lesion does not impair function and disfigurement is not considerable, particularly if the lesion presented after birth and/or is located in the neck region.

Finally, another reason to observe uncomplicated lesions for a period of time is related to anesthetic risk in infancy.¹⁷ Our centre has matriculated towards deferring elective surgery until after the child's first birthday based on our department of anesthesia's recommendations, and recent studies have suggested that waiting until the third birthday may be prudent.¹⁸

Authors' Note

Michael J. Phang contributed to the literature search, data collection, data interpretation, manuscript writing, and revision. Marija Bucevska contributed to supervision of manuscript writing. Claudia Malic contributed to the literature search, project idea, and study design. Douglas J. Courtemanche contributed to project idea, study design, and editing of manuscript. Jugpal S. Arneja contributed to project idea, study design, data interpretation, supervision of manuscript writing, and revision.

Declaration of Conflicting Interests

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References

1. Arneja JS, Gosain AK. Vascular malformations. *Plast Reconstr Surg*. 2008;121(4):195e-206e.

2. Behr GG, Johnson CM. Vascular anomalies: hemangiomas and beyond—part 2, slow-flow lesions. *AJR Am J Roentgenol*. 2013;200(2):423-436.
3. Ogita S, Tsuto T, Tokiwa K, Takahashi T. Intracystic injection of OK-432: a new sclerosing therapy for cystic hygroma in children. *Br J Surg*. 1987;74(8):690-691.
4. Poldervaart MT, Breugem CC, Speleman L, Pasmans S. Treatment of lymphatic malformations with OK-432 (Picibanil): review of the literature. *J Craniofac Surg*. 2009;20(4):1159-1162.
5. Smith MC, Zimmerman MB, Burke DK, Bauman NM, Sato Y, Smith RJ; OK-432 Collaborative Study Group. Efficacy and safety of OK-432 immunotherapy of lymphatic malformations. *Laryngoscope*. 2009;119(1):107-115.
6. Greinwald JH Jr, Burke DK, Sato Y, et al. Treatment of lymphangiomas in children: an update of Picibanil (OK-432) sclerotherapy. *Otolaryngol Head Neck Surg*. 1999;121(4):381-387.
7. Emery PJ, Bailey CM, Evans JNG. Cystic hygroma of the head and neck. *J Laryngol Otol*. 1984;98(6):613-619.
8. Peters DA, Courtemanche DJ, Heran MKS, Ludemann JP, Prendiville JS. Treatment of cystic lymphatic vascular malformations with OK-432 sclerotherapy. *Plast Reconstr Surg*. 2006;118(6):1441-1446.
9. Perkins JA, Maniglia C, Magit A, Sidhu M, Manning SC, Chen EY. Clinical and radiographic findings in children with spontaneous lymphatic malformation regression. *Otolaryngol Head Neck Surg*. 2008;138(6):772-777.
10. Xavier C, Emil S. Spontaneous resolution of lymphatic and venous malformations. *Eur J Pediatr Surg*. 2010;20(5):342-345.
11. Vasconcelos BN, Benez MDV, Bressan AL, Oliveira EF. Involution of a cystic hygroma of the face following local infection [in English, Portuguese]. *An Bras Dermatol*. 2011;86(1):135-137.
12. Bureqz H, Williams B, Chitte SA. Management of cystic hygromas: 30 year experience. *J Craniofac Surg*. 2006;17(4):815-818.
13. Charabi B, Bretlau P, Bille M, Holmelund M. Cystic hygroma of the head and neck—a long-term follow-up of 44 cases. *Acta Otolaryngol Suppl*. 2000;543:248-250.
14. Brock ME, Smith RJ, Parey SE, Mobley DL. Lymphangioma. An otolaryngologic perspective. *Int J Pediatr Otorhinolaryngol*. 1987;14(2-3):133-140.
15. Hogeling M, Adams S, Law J, Wargon O. Lymphatic malformations: clinical course and management in 64 cases. *Australas J Dermatol*. 2011;52(3):186-190.
16. Kennedy TL, Whitaker M, Pellitteri P, Wood WE. Cystic hygroma/lymphangioma: a rational approach to management. *Laryngoscope*. 2001;111(11 pt 1):1929-1937.
17. Ing C, DiMaggio C, Whitehouse A, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics*. 2012;130(3):e476-e485.
18. Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity—clinical implications of animal models. *N Engl J Med*. 2015;372(9):796-797.