Spontaneously resolved macrocystic lymphatic malformations: Predictive variables and outcomes

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INTRODUCTION: Lymphatic malformations are benign, low-flow vascular malformations that typically present at or near birth. Due to morbidity associated with operative treatment, non-operative treatment with injection sclerotherapy 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 whilst awaiting treatment. Herein 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, seven cases (11.5%; four females, three males) resolved spontaneously. Median age at malformation appearance was 2 years (range 0.6-5.5 years), with median age at resolution 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 to 15 years). All but one case was associated with local or upper respiratory tract infection antecedent to spontaneous resolution. Six of seven lesions were located in the neck.

CONCLUSION: Amongst 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 was higher than those of other series. While 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.

Key Words: Macrocystic lymphatic malformations; Treatment

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 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 tetradeyl sulphate, and doxycycline used (2). OK-432 is a lyophilized mixture of group A Streptococcus pyogenes first proposed in 1987 (3) 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 multi-center 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. While this case series is also retrospective in nature, this study aims to better
characterize the 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 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 Vascular Anomalies Clinic 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 subjects were identified through a review of the BC Children’s Hospital Vascular Anomalies Clinic (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 sixty-one patients presenting with MacLMs from 1999 to 2014, we identified seven cases (11.4%) where patients experienced clinical 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 three male patients were identified with a median age at malformation presentation of 2 years (range birth to 6.5 years). Two (2) 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, CT, or MRI. The median age at resolution was 4 years (range 10 months to 7 years), with median time from appearance to resolution of the malformation being 24 months (range 3 to 43 months). Median follow-up time was 4 years (range 1 to 15 years). All but one case was associated with an antecedent local or upper respiratory tract infection. Six of seven 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 two 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 of 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 preparation which leads to speculation that finding spontaneously resolving cases (86%) presented with malformations in the neck region. This is higher than the proportion of all MacLMs occurring in the neck region as indicated by 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).

**TABLE 1**

**Summary of patient variables and outcomes**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Gender</th>
<th>Age at Appearance (years)</th>
<th>Age at Disappearance (years)</th>
<th>Time to Resolution (months)</th>
<th>Follow-up (years)</th>
<th>Antecedent Event</th>
<th>Location</th>
<th>Planned Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>Yes, local</td>
<td>R. neck, posterior</td>
<td>OK-432</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>0.5</td>
<td>4</td>
<td>44</td>
<td>4</td>
<td>No</td>
<td>R. cheek/mandib-ular angle</td>
<td>OK-432</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>5</td>
<td>7</td>
<td>25</td>
<td>8</td>
<td>Yes, URTI</td>
<td>L. neck</td>
<td>OK-432</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>3</td>
<td>5</td>
<td>24</td>
<td>15</td>
<td>Yes, Strep. pharyngitis</td>
<td>R. flank</td>
<td>Not OK-432 amenable</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>Yes, URTI</td>
<td>R. neck</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>6.5</td>
<td>7.5</td>
<td>13</td>
<td>4</td>
<td>Yes, URTI</td>
<td>R. neck, posterior</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>0</td>
<td>2</td>
<td>24</td>
<td>2</td>
<td>Yes, suspected Strep. Infection</td>
<td>L. neck</td>
<td>OK-432</td>
</tr>
</tbody>
</table>

DISCUSSION

Out of seven cases of spontaneous resolution considered in this study, six cases (86%) presented with malformations in the neck region. This is higher than the proportion of all MacLMs occurring in the neck region as indicated by background literature, which varies from 45.48% (14,15) to 62% at most (16). All but one case in this series had history of an upper respiratory tract infection or local infection of the malformation event antecedent to spontaneous resolution, with one patient having group A Streptococcus pharyngitis confirmed on throat swab.

OK-432 consists of a lyophilized group A Streptococcus 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 seven cases involved singular/isolated lymphatic malformations which did not have significant functional impact for the patients. The above 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 x 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 x 2 x 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 years’ follow-up. Figure 1 represents the patient’s clinical photographs and ultrasound findings.
findings are fairly consistent with 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 non-spontaneously resolving MacLMs, or a multicenter study or prospective study to better characterize this population of patients.

CONCLUSION

Amongst the cases reviewed here, there was a common theme of upper respiratory tract or local infection antecedent to spontaneous resolution of MacLMs. Compared to literature, the proportion of malformations presenting after birth, and the proportion of malformations presenting in the neck region was 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. While 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).

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REFERENCES