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Doxycycline sclerotherapy for pediatric head and neck macrocystic lymphatic malformations: A case series and review of the literature

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ABSTRACT

Objective: (a) To evaluate the efficacy of doxycycline as a percutaneous sclerotherapy agent in pediatric head and neck macrocystic lymphatic malformations (LM) and (b) to review the literature with regard to recent developments in the treatment of lymphatic malformations using sclerotherapy.
Methods: We reviewed the medical records and imaging studies of all patients who underwent percutaneous sclerotherapy of macrocystic LM of the head and neck at our institution between June 2005 and May 2010. All studies were reviewed and procedures performed by a single interventional neuroradiologist using computed tomography (CT) guidance. LM were individually cannulated, the contents aspirated, and then injected with doxycycline at concentrations of 10–20 mg/ml. Response to sclerotherapy was determined clinically.
Results: Seven patients underwent a total of eight sclerotherapy treatments during the study period. Of the six patients with appropriate follow-up, 67% have experienced complete or near-complete clinical resolution of their LM (1243 days mean follow-up), while 33% have developed recurrent swelling after an initial response following a single doxycycline injection (53 days mean follow-up).
Conclusions: Our institutional results, in combination with recently published findings, support the moderate efficacy and excellent safety profile of percutaneous doxycycline sclerotherapy for macrocystic lymphatic malformations.

1. Introduction

Lymphatic malformations (LM) are benign tumors that are the result of abnormal embryogenesis of the lymphatic system [1]. They are common among vascular malformations in the pediatric population [2], and over 50% occur within the head and neck region [3,4]. These lesions are subdivided into three types: macrocystic lesions, which contain one or more cysts that are at least 2 cm^3 in volume; microcystic lesions, which contain cysts that are individually less than 2 cm^3 in volume; and mixed lesions, which contain both macrocysts and microcysts [4–6].

Due to their location in the head and neck, LM may cause significant functional and cosmetic morbidity. Although spontaneous resolution of these tumors may occur, the reported rate is disappointingly low at 3% [1,4]. As such, early treatment provides symptomatic, functional, and cosmetic improvement in otherwise persistent lesions [7]. Traditionally, surgery has been considered the standard of care for LM [1,8], but results are inconsistent. In 1995, de Serres et al. published a staging system that helped predict the results of extirpation based on lesion location. In this article, infrahyoid location and unilateral disease were correlated with improved outcomes. Surgery, however, was not without significant morbidity. They reported numerous complications, including cranial nerve injury, malocclusion, and poor cosmetic results; the rate of complications increased from 17% in stage I lesions to 100% in stage V lesions [9].

Molitch reported on 5 patients with lymphatic malformations in different parts of the body that were treated with percutaneous sclerotherapy using doxycycline, a broad-spectrum antibiotic from the tetracycline class, with size reduction or symptomatic resolution noted in all patients [10]. Since that time, numerous sclerosants have been reported in the literature to treat lymphatic malformations (refer to Table 1). Ethanol, sodium tetradecyl sulfate (STS), bleomycin, and OK-432 (Picibanil) have all been

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Table 1
Sclerosing agents used in the treatment of lymphatic malformations.

Doxycycline
Bleomycin
OK-432
Ethanol
Sodium tetradecyl sulfate (STS)
Ethibloc
Acetic acid

employed in treatment of head and neck LM based on experiences with other sclerotherapy procedures, and with varying but generally positive results [2,6,7,11]. These positive results have been consistent among macrocystic lesions; the results with microcystic lesions among the various sclerosants have been mixed [2,8,12,13]. For lesions refractory to sclerotherapy, surgery can be used as a salvage option; anecdotally, the use of sclerosants does not cause increased scarring and consequently does not make surgery more difficult [8]. Of the various sclerosants, doxycycline is gaining popularity, due to its low cost, ease of availability – particularly outside of research protocols – and excellent safety and efficacy profiles [4,13–15].

To verify the efficacy of doxycycline sclerotherapy, we conducted (a) a retrospective analysis of our experience with primary doxycycline sclerotherapy for pediatric head and neck macrocystic LM as well as (b) a review of the recent relevant sclerotherapy literature.

2. Materials and methods

Medical records and imaging studies of all patients who underwent percutaneous sclerotherapy of macrocystic LM of the head and neck between June 2005 and May 2010 were reviewed. Overall, seven patients presented during the study period and underwent eight sclerotherapy injections; 43% of the patients injected were female and 57% were male. Patients ranged in age from 1 month to 10 years at the time of treatment. Post-treatment follow-up for all patients averaged 725 days and ranged from 32 to 1511 days, with 2 patients lost to follow-up (Table 2).

All imaging studies were reviewed by a single interventional radiologist, who determined that the radiologic findings in all cases were consistent with a macrocystic lymphatic malformation. Most procedures (6 out of 8) were performed under general anesthesia. The fluid-filled space was cannulated using a small gauge needle under CT-guidance. Cystic fluid contents were aspirated and sporadically sent for cytologic and/or microbiologic analyses. 1–3 cm^3 of contrast material (Omnipaque 180, Amersham Health, Princeton, NJ) was then instilled to outline the cavity and determine any continuity with adjacent structures (Figs. 2 and 3). This was followed by an injection of doxycycline reconstituted in sterile water at a concentration of 10–20 mg/ml to fill the cavity (the highest doxycycline dose delivered in a single treatment was 233 mg). Nearly all patients (5 out of 7) were treated with peri-operative antibiotics with gram-positive coverage. No drains were placed. No immediate complications were noted. Procedures were performed on an outpatient basis, unless the patient was already hospitalized at the time of procedure.

3. Results

Of the seven patients in our study, one was lost to follow-up after his doxycycline treatment session. Of the six remaining patients who had at least one follow-up visit, two have undergone complete resolution of their LM (Figs. 1 and 4) without further incident (992 days mean follow-up) following an average of 1.5 treatments; the four remaining patients developed recurrent swelling. For three of the four patients with recurrent swelling, the recurrences coincided with episodes of infection. One of these three patients experienced swelling 4 years after sclerotherapy, which resolved without further incident following conservative treatment with oral antibiotics (now at 1477 days follow-up). Another of these three achieved near complete resolution, but he continues to demonstrate mild swelling of the right neck. He rarely develops infections in this area that result in increased swelling, but these resolve quickly with oral antibiotics. Because of the rarity of infection and the subtle nature of the swelling present at baseline, the family has opted to pursue conservative management only (now at 1511 days of follow-up). The last of the three patients – with swelling that was related to infection – required hospitalization for treatment with intravenous antibiotics. Although the swelling has since improved, the family is considering a second treatment with sclerotherapy (at 74 days follow-up). The patient who developed a recurrence of a fluid collection without an infectious cause (Patient #1 in Table 2) was available for only one follow-up visit at 32 days. This child is a part of the foster care system which has impaired our ability to regularly follow up with her.

With regard to complications, one of our patients presented to the emergency room after developing a cellulitis which required admission to the hospital for intravenous antibiotics. He responded well and was soon discharged on an oral antibiotic course. A different patient complained of pain at the time of procedure; he was one of only two patients who did not receive general anesthesia. Notably, after appropriate intra-operative pain control, his post-operative pain was unremarkable. None of the patients reported complications such as fevers, chills, or post-operative pain.

Table 2
Clinical presentations, outcomes, and follow-up. Age listed is age at the time of initial treatment.

	Age/sex	Lesion size and location	Stage	Number of treatments	Peri-procedural antibiotics	Clinical results	Follow-up (days)
1	3y/F	Right neck, level II: 8 cm × 5 cm × 6 cm	II	1	None	Recurrence	32
2	10y/M	Right parotid: 4 cm × 3 cm × 3.5 cm	II	1	Amoxicillin/clavulanate	Unknown	0
3	2m/M	Right submandibular space: 3.9 cm × 3.4 cm × 3 cm	IV	1	Clindamycin	Complete resolution	1115
4	7y/F	Left parotid and submandibular space: 4 cm × 4.5 cm × 4 cm	II	1	Cefazolin	Developed swelling with infection, now with complete resolution following conservative treatment	1477
5	1m/F	Right mandible: 6 cm × 2 cm × 5 cm	IV	1	Ampicillin/sulbactam	Recurrence with infection, plan for 2nd sclerotherapy treatment	74
6	2y/M	Left parotid tail: 4 cm × 6 cm × 2.5 cm	II	2	Cephalexin	Complete resolution	868
7	3y/M	Right neck: 7 cm × 6 cm × 4 cm	II	1	None	Near complete resolution, develops mild infection rarely that responds to oral antibiotics	1511