

Sclerosing treatment of lymphangiomas with OK-432

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Abstract

Over a period of seven years, 15 patients (aged from birth to 15 years; median 22 months) with lymphangioma were treated with OK-432; they received a mean of three injections each. Ten received OK-432 as first line treatment; five were treated after surgery (three had a residual lymphangioma after incomplete removal and two had a late recurrence). OK-432 proved to be effective for primitive as well as for residual and recurrent lymphangioma. Seven cases were macrocystic; complete regression was obtained in all. Five cases were microcystic: two had more than 50% regression, and three less than 50%. Three cases were mixed, with both large and microscopic cysts: one had more than 50% regression, and two less than 50%. These last two cases underwent surgery after the sclerosing treatment. The results obtained were excellent in 100% of macrocystic cases; a shrinkage in size was obtained in all microcystic cases. OK-432 is therefore proposed as a first line option for treatment of lymphangiomas.

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Surgical treatment of lymphangiomas is complicated by a high incidence of recurrence and local nerve damage; alternative modes of treatment are therefore under investigation.

Intralesional sclerosis of lymphangiomas with OK-432, a streptococcal derivative (Chugai Pharmaceutical Co, Tokyo, Japan), was introduced by Ogita, initially for unresectable cases.¹ He subsequently extended his indications and proposed OK-432 as first line treatment in all cases.² Apart from his series,

only a few children have received this treatment because the drug is not easily available outside Japan.³⁻⁷ We therefore believe it of value to report our own experience with this therapy.

Materials and methods

From 1992 to 1998 we treated 15 patients with OK-432. Age at treatment ranged from birth to 15 years (median 22 months). Seven lesions involved the neck, two the cheek, two the face-mouth-neck, two the trunk, and two were localised in the mediastinum. All patients were investigated by ultrasound; some with deep extension of the tumour also underwent computed tomography or magnetic resonance imaging. The lesions were classified according to the diameter of the majority of cysts as macrocystic (greater than 1 cm), microcystic (less than 1 cm), or mixed, when both large and microscopic cysts were present. OK-432 was injected according to the method of Ogita⁸: 0.1-0.2 mg/dose every two months. The injections were performed under sedation, with ultrasound guidance in some cases to localise the larger cysts in which to inject the drug.

Results

Results were considered excellent when there was complete regression of the lymphangioma, good when the regression was estimated to be more than 50% of the initial volume, and poor when it was less than 50%.

Ten children received OK-432 as first line treatment. Four cases were macrocystic and had excellent results after one to three injections. Three cases were microcystic: two regressed well after four injections, and one, which was unresectable, had a poor regression after three injections. Three cases were mixed: one child had a good result after two injections, the other two (cases 9 and 10) had a poor result even after multiple injections, as only the large

Table 1 Patient data and response to treatment

Case	Sex	Age	Site*	Previous surgery	Type	Size (cm)	Injections (n)	Results
1	F	Newborn	N	No	Macro	4 × 3	3	Excellent
2	F	12 months	N	No	Macro	5 × 4	1	Excellent
3	F	21 months	N	No	Macro	5 × 4.5	2	Excellent
4	F	15 years	N	No	Macro	5 × 4	1	Excellent
5	M	5 years	N	Yes	Macro	6 × 5	1	Excellent
6	F	4 months	N-M	Yes	Macro	3.8 × 3.7	1	Excellent
7	F	3 years	N-M	Yes	Macro	4 × 2.5	2	Excellent
8	F	33 months	N	No	Mixed	3 × 2.7	2	Good
9	F	Newborn	F-m-N	No	Mixed	Huge	16	Poor, surgery
10	F	15 months	N	No	Mixed	5.5 × 5	3	Poor, surgery
11	F	22 months	Cheek	No	Micro	3 × 0.9	4	Good
12	F	12 months	Chest	No	Micro	5 × 4.5	4	Good
13	M	32 months	Cheek	No	Micro	4 × 2	3	Poor
14	F	28 months	Chest	Yes	Micro	7 × 5	1	Poor
15	M	9 years	F-m-N	Yes	Micro	Huge	9	Poor

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*F, face; M, mediastinum; m, mouth; N, neck.

cysts disappeared, while the microcystic component remained unchanged. These two children underwent surgical resection after failure of sclerosing treatment; no adhesions were found around the tumour, and a thick capsule surrounding the lesion made the resection easier to perform than expected.

Five children had already had surgery as first line treatment: three had a residual lymphangioma after incomplete removal and two had a late recurrence. Three of these five cases were macrocystic and had excellent results after one or two injections. The other two cases were microcystic; they had poor results after one to nine injections and refused further treatment (table 1).

Almost all children had fever and signs of local inflammation for one to four days following the injections; in one patient a feeding tube was needed for a couple of days because of cervical swelling. There have been no serious complications to date. Only one child has had a recurrence of the lymphangioma one year after treatment; this resolved spontaneously.

Discussion

Resection of a benign tumour, such as a lymphangioma, is justified because of the complications related to its presence, some of which are extremely serious. Besides the fact that it rarely regresses spontaneously, causing aesthetic concern, it can become infected; this may be life threatening and it can cause airway and feeding problems. Cases have recently been reported of severe osteolysis caused by a lymphangioma.⁹

In the past lymphangiomas were always treated surgically, and even today, with the many treatment options available, most surgeons believe surgery to be the first choice. Sparing of neural and vascular structures is one of the goals of surgery, but no specific surgical technique has been developed. Therefore, even in the most expert hands, surgery still carries a complication rate as high as 12–33%, and a recurrence rate of 15–53%.^{10–13} Moreover, it is almost never radical at the first attempt and, hence, needs to be staged.

Throughout the years multiple non-surgical strategies have been attempted in order to cure the lesion with as few complications as possible. Radiotherapy was used in the early 1920s and 1930s, but owing to complications such as oesophagitis, tracheitis, and malignancy, it was soon abandoned. In the 1990s a combined radiochemotherapeutic approach was proposed, with good results for selected cases of life threatening haemolymphangiomas. Chemotherapy, besides the protocol described above, has been reported in a few patients with mixed results and should be reserved only for those not otherwise treatable cases.

CO₂ and Nd-Yag lasers are more extensively used for localised laryngeal lymphangiomas.¹⁴ Use of an argon beam coagulator has been reported in a 13 year old girl with life threatening total abdominal lymphangiomatosis.¹⁵

The idea of treating lymphangiomas with sclerosing agents is an old one. At the beginning of the century it was noted that after

spontaneous infection, lymphangiomas could shrink or even completely regress. The mechanism involves destruction of the epithelium lining the cystic spaces, with subsequent decrease in lymph fluid production and collapse of the cysts. Many different drugs were used to mimic what may occur spontaneously, but none worked as expected. One of the main problems with sclerosing drugs is their tendency to spread outside the lesion once injected. This can cause unpredictable damage to surrounding structures and make subsequent surgery more difficult. Hence surgical treatment remained the first option.

In 1977 bleomycin,^{16 17} an antibiotic known to have some antitumoral activity, was proposed as a new sclerosing agent for cystic hygroma. Good or excellent results have been shown in up to 88% of cases.¹⁸ However, bleomycin can rarely cause pulmonary fibrosis.

Recently, an alcoholic solution of zein (Ethibloc) has been proposed as a sclerosing agent for lymphangioma.^{19 20} After its successful utilisation in venous malformations this solution was injected into the lymphatic lesions in more than 80 patients. Overall the results were good or excellent in almost 60% of cases. Unfortunately it was also noted that Ethibloc can be expelled through the skin for weeks or months after injection, affecting the final aesthetic result.

In 1987 Ogita published his results from a trial using OK-432 in children,⁸ reporting total regression of the lesion in eight of the nine cases treated. He did not encounter any major complications nor late recurrence, and no surgery was needed. The preliminary positive results have been confirmed recently.² The author reported 64 patients with an excellent outcome in 44% and a good outcome in 15.6%. If the cases presenting with the macrocystic type, which is known to be more favourable, are examined separately, 92% of the patients showed complete and stable regression.

Encouraged by these promising results, in 1992 we began to treat our patients with OK-432. Since then, we have treated 15 patients, of whom 10 had an excellent or good result. If the macrocystic types were considered separately, all were completely cured using OK-432 alone. Microcystic and mixed type lesions responded less favourably, but some shrinkage could be appreciated in all patients. Therefore we suggest OK-432 is considered as the first option in all lymphangiomas, regardless of the age of the patient, and the size and type of the lesion. We disagree with the proposal by Smith,⁶ based on only six cases, that suggests limiting sclerosing treatment to macrocystic forms.

In our experience OK-432 proved to be effective for primitive as well as for residual and recurrent lymphangiomas. It is an undoubtedly useful procedure both when radical excision is surgically challenging and when it is technically feasible, as it is much less invasive and avoids skin scarring. Long term results are not yet available, but there is no evidence of late adverse effects so far; our first case is now seven

years post-treatment and no complication has been encountered.

Surgical excision, once considered the treatment of choice, should be reserved for those cases in which the sclerosing agent is insufficient. It is better to postpone it until after the injection of OK-432, in light of the fact that pretreatment does not adversely affect the subsequent surgical procedure.

In conclusion, we consider OK-432 safe and easy for the treatment of lymphangiomas, with the obvious exception of those cases in which the airway is involved and for which a multidisciplinary approach should be considered.

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