Treatment of lymphangiomas by means of sclerotherapy with OK-432 (Picibanil®) is safe and effective

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Abstract
Congenital cystic lymphangiomas (CCL) or lymphatic malformations (LMs) are benign malformations due to a developmental disorder of lymphatic vessels. The most frequent localization of lymphangiomas is the neck and head region. The fact that the lesions usually have no spontaneous regression, tend to augment in size and may cause life-threatening complications such as occlusion or infiltration of neighbouring organs and structures, underlines the need of an early adequate therapy. Surgical excision used to be the first-line treatment of lymphangiomas. However, complete excision often is not possible. Besides surgical excision, sclerosant therapy of these lesions by intracavitary injection of OK-432 (Picibanil®), a lyophilized mixture of group A Streptococcus pyogenes, is a common therapeutical option.
In our hospital we used it for sclerotherapy in 37 patients, with a median age of 6.9 years (range 0.5-39.9 years). The median follow-up period was 2.5 months (range 0.7 – 56.7 months). The lymphangiomas were localized in the head and neck region (n=25), the thorax/abdomen (n=6) and extremities (n=6). The majority of patients had 1 injection with OK-432 (n=28), five patients had 2 injections, three patients had 3 injections and one patient had more than 3 injections. The most common complications were swelling (89%), fever (81%), redness at the injection site (81%) and pain (73%). The response to therapy was excellent or good in 32 patients (86.4%), 2 patients had a medium

response and 3 patients did not show any response. The clinical reaction after the instillation of OK-432 is not predictive for the quality of outcome.
Sclerotherapy is recommended primary for macrocystic lymphangiomas. The application is safe and without serious side effects.
Parents and patients prefer local sclerotherapy versus surgery as it has less complications.
In our hands it is the first-line therapy in the treatment of lymphatic malformations.

Keywords : Lymphatic malformations (LMs); OK-432 (Picibanil®); sclerotherapy;

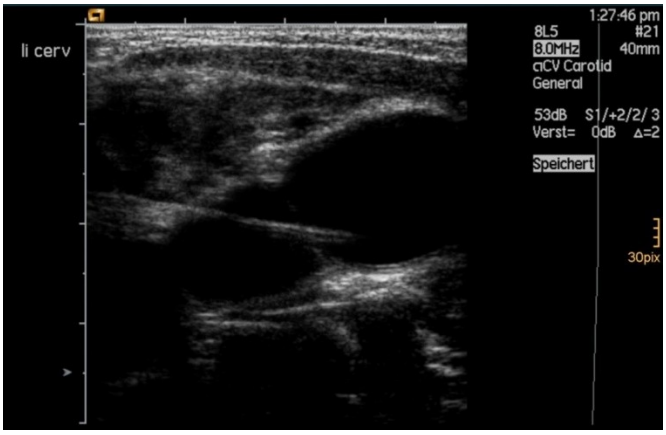
Introduction

Lymphatic malformations (LMs) are one type of vascular malformations and consist of masses of abnormal lymphatic vessels that occur in one out of 2000 to 4000 live births [1,2] and frequently involve the head and neck, oral cavity/pharynx, thorax and/or mediastinum. Occasionally they affect vital functions, frequently they cause disfigurement.
They can be characterized as macrocystic (diameter > 1 cm), microcystic (diameter < 1 cm) or mixed cystic lesions [2,3]. On the basis of their histological appearance, lymphangiomas are classified as capillary, cavernous or cystic and contain dilated lymphatic vessels in size ranging from small channels to large cysts. Often the lesions are a combination of these subtypes and may also contain hemangiomatous components.
The principal goal of LM management is restoration or preservation of functional and aesthetic integrity. The standard treatment of lymphatic malformations has been ablative with variable success, sometimes necessitating multiple treatments and long-term management [3,4,5].
All treatment is based on a thorough initial assessment to detect the degree of functional impairment and/or disfigurement. When there is no significant functional deficit, treatment can be delayed well past infancy. Treatment timing relative to the age of the patient is somewhat debatable. LMs of small dimensions, without functional impairment or cosmetic disfigurement, do not necessarily require treatment. The possibility of spontaneous regression in low-stage macrocystic LM suggests that observational monitoring may also be appropriate in children with asymptomatic cervical LM, although this option is rare [6].
Even small LMs can suddenly and impressively expand in size in the setting of intra-LM hemorrhage, infection or trauma. Extensive cervicofacial LMs have the potential for aerodigestive tract compromise, in addition to causing long-term sequelae such as mandibular distortion, dental malocclusion and speech impairment [7].
Complete and meticulous surgical excision is the textbook recommendation for the primary approach to lymphangiomas. However, complete excision is often impossible due to the risk of damage to vitally or functionally important surrounding structures. In addition, the cosmetic outcome after such radical surgery may be unacceptable, especially in children. To avoid complications of surgical therapy, several treatment options, including laser therapy, interferon alpha, propranolol, rapamycin, Kampo medicine and various intralesional sclerosing agents such as hypertonic saline, ethanol, bleomycin and OK-432 have been used to treat lymphangiomas.
OK-432 (Picibanil, Chugai Pharmaceutical Co., Ltd. Tokyo, Japan) is a freeze-dried biological product that is prepared from the Su strain of Streptococcus pyogenes (group A) by treatment with benzyl-penicillin and heat. Heating in the presence of penicillin at 37°C for 20 min and 45°C for 30 min increases the antitumor activity of the Su strain and eliminates its toxin-producing capacity. Since OK-432 is not subjected to further treatment, such as isolation, extraction or purification, the bacterial cells remain intact. However, proliferative activity is lost and streptococcal infection does not occur when it

is administered to humans. Klinische Einheit (KE) is used as a unit of measurement for OK-432 doses. One KE corresponds to 0.1mg of freeze-dried streptococci containing approximately 1 x 10^8 cells [8]. In Japan, OK-432 was approved as an immunotherapeutic agent for cancer by the Ministry of Health and Welfare in 1975.
In the initial stage of development, OK-432 was considered to induce direct inhibition of RNA synthesis in tumor cells. Other reports of a direct action on tumor cells also appeared, but currently the main action is considered to be via stimulation of host immunity [7]. Its good efficacy in infantile LMs was first confirmed by Ogita et al in 1987 [9]. The mechanism of OK-432 remains confined within the malformations after injection and stimulates lymphatic endothelial cells, resulting in obliteration of lymphatic channels with minimal local fibrosis [10].
In lesions which are near to the aero-digestive tract the patient must be closely observed in the postoperative period and the medical staff has to be aware of the possibility of local compression due to swelling. Also it is important to be aware of the possibility of allergy to benzyl-penicilline.

Materials and methods

In a retrospective study we analyzed 37 patients (30 children, 3 adolescents and 4 adults) who were diagnosed with lymphangioma and subsequently treated with OK-432 (Picibanil®, Chugai Pharmaceutical Co, Tokyo) between October 2000 and November 2021.
The diagnosis was made by ultrasound or ultrasound and MRI in combination.
The procedures were performed either in general anesthesia (first choice) or in local anesthesia. Under sterile conditions and under ultrasound guidance one or more cysts were punctured and drained and afterwards an equivalent refilling of the cysts with 0.02 to 0.2 mg OK-432 (0.01 mg/ml in normal saline solution) was carried out (Fig.1).



(a)


(b)

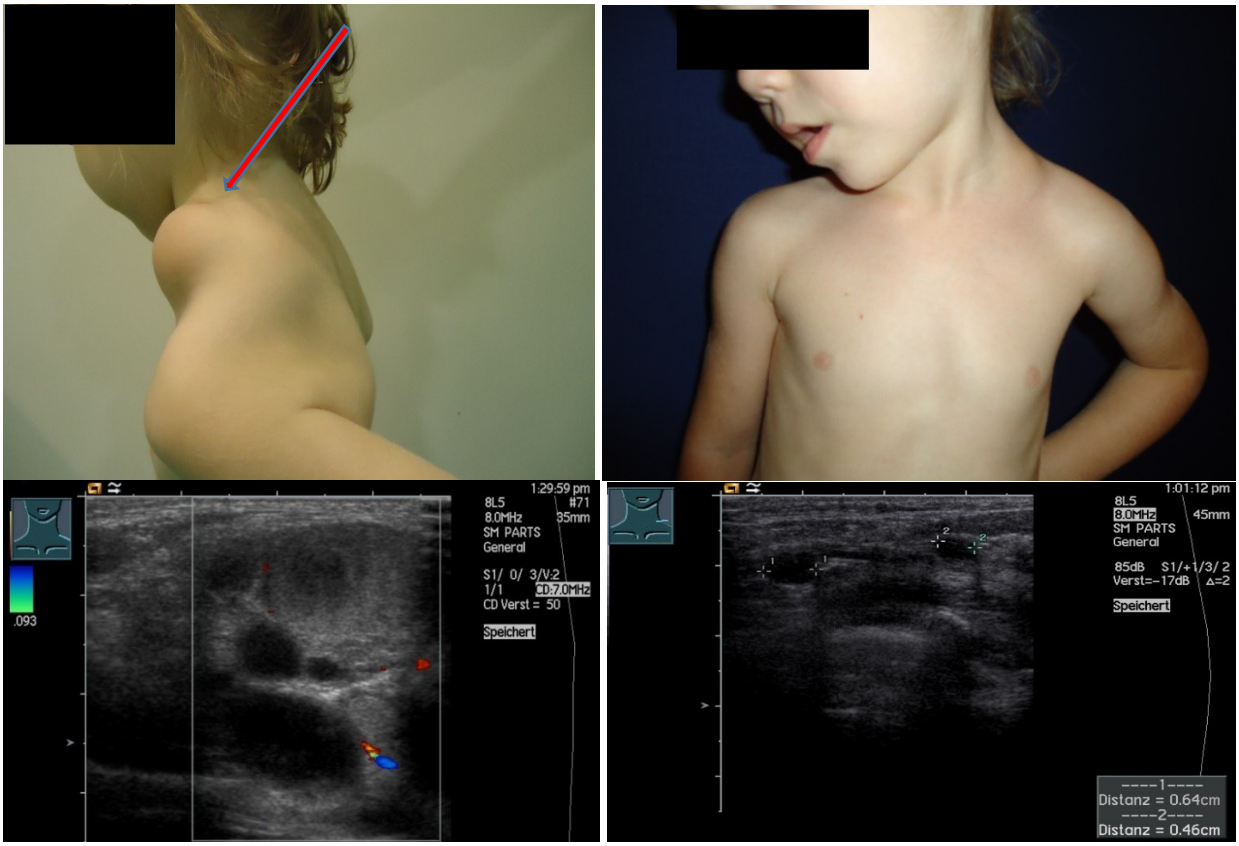
Figure 1 – Ultrasound injection of OK -432 into lymphangioma (a), after aspiration (b)

The majority of patients had 1 injection with OK-432 (n=28), five patients had 2 injections, three patients had 3 injections and one patient had more than 3 injections.
In the postoperative period the patients were observed for complications for one to three days in the hospital.
For the interpretation of the results we used the Acevedo classification, according to which excellent results mean complete regression of the lymphangioma, good results if regression is more than 50 %, poor results if regression is under 50 % and no response [2].
We also wanted to show if the symptoms after treatment with OK-432 had a prognostic value for the outcome.

Data were expressed as mean and range. Statistical analysis was performed using Fisher's exact test. A P value of less than .05 was considered statistically significant.
The study was approved by the ethics committee of the government.

Results

The median age in our study group was 6.9 years (range 0.5-39.9 years). The median follow-up period was 2.5 months (range 0.7 – 56.7 months). The lymphangiomas were localized in the head and neck region (n=25), on the thorax/abdomen (n=6) and extremities (n=6).
The most common complications after treatment were fever (81%) for a few days and signs of inflammation (swelling (89%), redness at the injection site (81%) and pain (73%) for up to some weeks postoperatively). There was no airway obstruction complication because of the injection treatment.
Eight patients (21.6%) had an excellent response to therapy, 24 patients (64.8%) had a good response, 2 patients (5.4%) had a poor response and 3 patients (8.1%) did not show any response (Fig. 2).



(a) 4 days post-injection ***(b)*** 2 month post-injection

Figure 2 4-year-old girl with near complete regression at 2 months post-injection of OK-432

A Fisher's exact test showed that there was no statistical association between the symptoms after the injection and excellent/good outcome ($P < .05$).

Discussion

Lymphangiomas may cause marked disfigurement, recurrent infections, respiratory obstruction, malocclusion, dysphagia, dysphonia and dysarthria as a result of the infiltration and compression of neighbouring structures. Spontaneous regression is rare and sometimes followed by recurrence [11]. Histologically, these lesions are composed of dilated lymphatic vessels with one or two endothelial layers, with or without an adventitial layer. These dilated lymphatics can vary in size, depending on the location and surrounding tissues, representing the basis for classification. Cystic hygromas arise from lymphatic tissue in areas where expansion can occur. Cavernous lymphangiomas are found in areas such as the tongue and floor of the mouth.

In most cases diagnosis is not difficult. The neoplasms are usually characterized by the presence of a soft, compressible and ill-defined mass. The anterior triangle of the neck has been indicated as the most common site. Cystic hygroma may be localized in the parotid area, and is the second most common congenital mass of this area [11].

Ultrasound and MRI can be used to define the relationship of the lesion with the neighbouring structures and to help plan therapeutic strategies.

After Ogita reported the results of OK-432 sclerotherapy in lymphangioma in 1987, many reports around the world have concluded that OK-432 is a safe and effective treatment modality for lymphatic malformations. Also OK-432 can be used after surgery in case of recurrence of the lymphangioma. It was also used to treat a wound–healing impairment with good results [12].

Furthermore, many physicians have administered OK-432 sclerotherapy to ranula and branchial cysts and achieved successful results. OK-432 seems to be safer and more effective than other sclerosing agents such as boiling water, hypertonic saline, ethanol, tetracycline, cyclophosphamide, sodium morrhuate, and bleomycin [13]. Although the complication rates with treatment by these sclerosing agents have been minimal, limited success and unpredictable local scarring, as well as systemic side effects caused by spread of the agents beyond the endothelial lining of the lesion, have been observed. Bleomycin, in particular, can cause serious side effects, including fibrosis of the lung [13,14].

The precise mode of action of OK-432 has not been fully understood, but it seems to be related to an immunomodulatory effect. Picibanil induces cytokines and activates many inflammatory cells, such as neutrophils, macrophages, lymphocytes and T-cells. The cytokines induce strong local inflammatory reactions in the cyst wall, resulting in fluid drainage, shrinkage, and fibrotic adhesion of the cyst [15]. During the early postinjection period, acute inflammatory cells (neutrophils and macrophages) predominate, but 4 days later activated lymphocytes and natural killer cells represent the majority and TNF and IL-6 levels are elevated. Another proposed mechanism is that picibanil induces apoptosis of the lymphatic endothelium. This hypothesis concurs with the finding that the local inflammatory reaction induced by picibanil does not involve the skin or cause scar formation. No necrosis is seen histologically although the OK-432 induces inflammation and activation of IL-6 and TNF alfa [16,17,18]. OK-432 can diffuse even into small cysts. This might explain why OK-432, unlike other sclerosing agents, has effect even on small-cystic LM.

OK-432 leads to complete or near-complete response in macrocystic lesions, with a lower degree of response in mixed, microcystic lesions or polycystic lesions, which concurs with our findings [19,20,21,22,23].

Which factors favor a good response or define a non-responder is unclear. Reismann concludes that a dynamic TLR4-expression may represent a predictive parameter [24].

Statistically, we could not confirm that a good reaction after the instillation of OK-432 with swelling, reddening, pain and fever is associated with an excellent or good outcome.

No major complications were encountered in our patients, the treatment was well tolerated and with no local scarring and it had a high rate of excellent/good response (86.4 %), so that in our hands it is the

first-line therapy in the treatment of lymphatic malformations. Parents and patients prefer local sclerotherapy versus surgery as it has less complications.

Conclusions

Sclerotherapy of lymphatic malformations with OK-432 achieves excellent to good clinical response in the majority of patients. The application is safe and without serious side effects. Swelling, redness at the injection site, low-grade fever and pain are to be expected after the therapy with OK-432.
A low recurrence rate and good response to repeated injections in recurrent or primary failed cases yielded good long-term response. To summarize, we found that Picibanil is a good sclerotherapeutic agent with only minor complications and high long-term efficacy for lymphangioma. We therefore suggest that picibanil sclerotherapy should be the first-line treatment for macrocystic and mixed type lymphangiomas.

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