CardioVascular and Interventional Radiology

Published Online: 5 December 2002

Cardiovasc Intervent Radiol (2003) 26:31–36
DOI: 10.1007/s00270-002-1980-3

Treatment of Lymphangiomas with OK-432 (Picibanil)

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Abstract

Purpose: To determine the efficacy of OK-432 sclerotherapy in the treatment of lymphangiomas.
Methods: The treatment was begun for 14 patients with lymphangioma. The age range of the patients at the time of the first injection was from 10 months to 42 years. Eleven of the lesions involved the head and neck region, two the thorax and one was localized in the extremity. Prior to treatment all patients were investigated with either magnetic resonance imaging, computed tomography, ultrasound or a combination of these modalities. The injections were performed with ultrasound and/or fluoroscopic guidance. Eight patients received OK-432 as first-line treatment; five were treated after surgery and one after medical therapy. On average, 2.2 intracystic injections were performed per patient. Nine of the lesions were macrocystic and five were mixed lesions.
Results: Eleven patients showed complete or marked response to the OK-432 sclerotherapy, two patients had moderate shrinkage of their lesions and only one patient showed no response to therapy. Macrocystic lesions showed the best response to therapy. Those patients who received OK-432 as first-line treatment showed complete or marked response.
Conclusion: It was found that treatment of lymphangiomas with OK-432 was safe and effective.

Key words: Lymphangioma—Arteriovenous malformations—Sclerotherapy—OK-432

Lymphangiomas or cystic hygromas are relatively rare congenital malformations of the lymphatic system. Ninety percent of lymphangiomas are diagnosed in children younger than 2 years; almost half of them are present at birth [1–3]. Approximately 75% of lymphangiomas are located in the neck region, some of them growing into the mediastinum. Lymphangiomas located purely in the mediastinum appear rarely [4]. The precise pathogenesis of lymphangiomas has not been defined. Anatomically they are fluid-filled sinuses lined by vascular endothelium, obviously as a result of erroneous embryogenesis [1, 5]. Lymphangiomas may also exist in combination with other vascular anomalies [5, 6]. On the basis of average sinus size lymphangiomas can be subclassified as capillary, cavernous or cystic, although a combination of these subtypes is also common. Subclassification as microcystic or macrocystic lesions is clinically relevant when identifying lesions that may respond to specific forms of therapy [7]. In the diagnosis of lymphangiomas various imaging modalities may be needed. Magnetic resonance imaging (MRI), color Doppler ultrasound and computed tomography (CT) are the most precise methods in the diagnosis of lymphangiomas and differential diagnosis from other vascular malformations.

Spontaneous regression occurs in only about 6% of lymphangiomas. Generally they are asymptomatic and nontender tumours that grow slowly [1–3]. As their size increases they may cause cosmetic impairment or interfere with breathing and swallowing [8]. Bleeding and infection can rapidly increase the size and threaten vital functions [9]. The most widely accepted treatment is surgical excision, even today, with the many treatment options available. However, due to the infiltrating growth of the tumor, complete excision is seldom achieved. Nonsurgical treatment with diathermy and radiation therapy has been used [10], as well as intralesional injection of various sclerosing agents such as alcohol, boiling water and bleomycin [7, 10, 11].

Recently there have been promising results from treating lymphangiomas of the head and neck region with a new sclerosant, OK-432 (Picibanil) [12]. OK-432 is a lyophilized biological preparation containing the cells of *Streptococcus pyogenes* Su-strain treated with benzylpenicillin. When injected into the cystic spaces it produces sclerosis that does not spread outside the lesion. Adverse effects of treatment

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Table 1. Results of OK-432 therapy

Patient no.	Sex/age at first injection	Location of lymphangioma	Symptoms	Earlier treatment	Type	Size (Max. diameter, cm)	No. of sessions	Total dose of OK-432 (ml; 0.01 mg/ml)	Follow-up time	Volume reduction
1	F/2 yr 8 mo	Thorax, axilla	Sw, pain	None	Macrocystic	12	1	6	2 yr 4 mo	Complete
2	F/6 yr 3 mo	Thorax	Sw	None	Macrocystic	8	1	4	1 yr 2 mo	Complete
3	M/12 yr 11 mo	Neck	Sw	None	Macrocystic	5	2	10	1 yr 1 mo	Complete
4	M/9 yr 7 mo	Neck	Sw	None	Macrocystic	11	1	10	1 yr	Complete
5	M/42 yr	Neck	Sw	None	Macrocystic	10	1	8	11 mo	Complete
6	M/10 mo	Neck	Sw, dyspnoea	None	Macrocystic	8	4	32.5	1 yr 6 mo	Marked
7	M/5 yr 6 mo	Neck	Sw	Surgery	Macrocystic	3	2	2.5	1 yr 1 mo	Marked
8	F/23 yr 1 mo	Neck	Sw	Surgery	Macrocystic	5	2	18	2 yr 8 mo	Moderate
9	M/1 yr 3 mo	Upper extremity	Sw	Surgery	Macrocystic	15	1	18	1 yr 8 mo	No response
10	M/2 yr 6 mo	Neck	Sw	None	Mixed	4	2	7	2 yr 7 mo	Complete
11	F/2 yr 5 mo	Neck, base of tongue	Sw, dyspnoea	Surgery	Mixed	10	7	54.5	2 yr 10 mo	Marked
12	F/3 yr 2 mo	Orbit, cheek, palate	Sw, exophthalmus	Interferon	Mixed	5	4	11	1 yr 3 mo	Marked
13	F/11 yr 11 mo	Cheek	Sw	None	Mixed	7	1	5	9 mo	Marked
14	M/13 yr 7 mo	Neck, skeletal	Sw	Surgery	Mixed	8	2	25	1 yr 6 mo	Moderate

Sw, swelling; yr, years; mo, months.

are limited to mild post-injection pyrexia [10]. The first results of intralesional injection of OK-432 as treatment for lymphangioma were reported in 1987 [13]. In our institution we began to treat with OK-432 in January 1999. This kind of treatment for lymphangiomas is experimental and should not be used in centers where there is only minimal experience with vascular malformation in general. In this article we report our results using OK-432 as treatment for lymphangiomas.

Materials and Methods

Between January 1999 and February 2001 OK-432 treatment was begun for 14 patients with lymphangioma (Table 1). The patients had been chosen for this therapy because of the clinical signs and symptoms they had. Prior to OK-432 treatment three of the patients were investigated with MRI, two with ultrasound and nine with both these modalities. In addition one arteriography, one venography and one CT examination were performed. The diagnosis was based on the typical findings of lymphangioma: fluid-filled sinuses without flow. Five patients had histologic verification. The lesions were classified as macrocystic (diameter of the cysts greater than 2 cm), microcystic (less than 2 cm) or mixed. This classification of lesions was based on measurements from MRI and ultrasound examinations. This classification has also been used in the previous reports [10, 14–16]. No basic laboratory tests were carried out prior to treatment.

There were six females and eight males with a mean age of 9 years and 10 months at the time of the first injection (range 10 months to 42 years). Two of the patients were under 2 years of age and two over 18 years. Eleven lesions involved the head and neck region, two the thorax and one was localized in the extremity. One patient also had skeletal involvement, two patients had a combination of lymphangioma and vascular malformation, one with Klippel–Trenaunay syndrome and the other with a capillary-venous malformation of the tongue. Five of the patients had previously received surgical treatment and one interferon therapy.

The injections were performed with ultrasound and/or fluoroscopic guidance. Some of the superficial injections were done after fluid aspiration, without any radiological guidance. As in previous reports, the concentration of OK-432 was 0.01 mg/ml (0.1 mg of OK-432 per 10 ml of physiologic saline). The solution was used in this concentration in all but one of the treatment sessions. A solution of half this concentration was used once for a patient who had had a remarkable reaction after the previous injection. After the needle was introduced into the cyst, contrast was injected to verify needle placement in the lesion, to image the possible communication of the intralesional spaces and determine the amount of OK-432 to be injected. Fluid was aspirated from the cystic space and the same volume of OK-432 solution was injected. If this was not possible, approximately half the estimated volume was injected. If the intralesional spaces did not communicate in the previous contrast injection, OK-432 was injected at several sites. The maximum volume injected at one treatment session was 10 ml. The treatment of children was performed under general anesthesia; for adults only local anesthesia was needed. No preventive medication with antibiotics was used because it would have suppressed the effect of the treatment. Antibiotics were used only once when there was a reaction with symptoms and signs of infection.

The interval between sessions was scheduled to be 1 month. If the patient was not in good clinical condition prior to treatment (having flu for example), the treatment session was delayed. The possible side-effects were recorded. If the patient responded to therapy, treatment was continued until his or her clinical condition was considered to be satisfactory.

The response to treatment was assessed clinically and graded radiologically with the same modality as prior to treatment. Reduction in lymphangioma volume was recorded as complete, marked (more than 50% of the initial volume), moderate (less than 50% of the initial volume) or no response. The patients had clinical follow-ups 1, 3, 6 and 12 months after the last treatment session. Imaging control was done after the treatment was considered to be finished, or during the follow-up in cases of no response to the treatment or a suspicion of some kind of complication.

Table 2. Volume reduction in correlation with type and earlier treatment of lymphangiomas

	Mean size (cm)	Mean no. of sessions	Mean total dose of OK-432 (ml; 0.01 mg/ml)	Volume reduction		Total
				>50%	<50%	
Lymphangioma type						
Macrocystic	8.6	1.7	12.1	7	2	9
Mixed	6.8	3.2	20.5	4	1	5
Earlier treatment						
None	8.1	1.6	10.3	8	0	8
Surgery	8.2	2.8	23.6	2	3	5
Interferon	5	4	11	1	0	1

Results

The lymphangioma diminished to an insignificant scar residue in six patients, five patients had marked shrinkage, two patients had moderate shrinkage but one patient showed no response. Four of the patients have not yet completed their therapy, but in all of them we have already achieved reduction in the size of the lesion. In the eight patients who had more than one injection the mean number of treatments was 2.2 (range 2–7 injections). The mean time of hospital stay was 2.8 days. For those patients who have completed their therapy the mean time for treatment was 6 months 20 days.

Nine of the lymphangiomas were defined as macrocystic and five as mixed lesions. None of our patients had a microcystic lesion. Complete or marked reduction in volume was achieved in 11 patients (79%), with complete reduction dominating among patients with a macrocystic lesion (5 of 9, i.e. 56%) and marked reduction among mixed lesions (3 of 5, i.e. 60%). The favorable results among patients with macrocystic lesions were obtained with fewer sessions and with smaller amounts of OK-432 than those among mixed lesions. All patients who received OK-432 as first-line treatment had complete or marked response. After surgery or interferon therapy the results were not so favorable, in spite of a greater number of sessions and larger volumes of OK-432 (Table 2).

Slightly elevated temperature in the first few days after injection was recorded in 11 patients. One patient (No. 6) developed an intense cervical swelling after the first injection. No other complications have been encountered.

Two of the patients were treated surgically after OK-432 therapy. One patient (No. 8) had macrocystic lymphangioma in the submandibular area. She had been treated surgically already before OK-432 injections. After two OK-432 injections her lesion showed only moderate regression. Thereafter she was treated surgically but already there is recurrence of the lesion and new surgical treatment is being planned. The other patient (No. 9) has Klippel-Trenaunay syndrome, and his venolymphatic lesion in the upper extremity has been surgically treated. In this operation the venous component was moderately reduced in size. One patient (No. 11) has a combination of lymphangioma in the cervical region and macroglossia (capillary-venous malformation in the tongue). The latter has been treated with repeated transcatheter embolizations with polyvinyl alcohol particles.

After a mean follow-up period of 1 year 8 months after the first OK-432 injection there have been no recurrences (range 9 months to 2 years 10 months).

Discussion

The classification, diagnosis and treatment of vascular anomalies are still in a phase of turbulent development. We have found the classification system of Mulliken and Glowacki to be the most effective in clinical practice [17]. This separates vascular anomalies into vascular malformations and hemangiomas. Vascular malformations are congenital maldeveloped vascular structures without endothelial proliferation. On the basis of their pathologic structures vascular malformations are subcategorized as arterial malformations, capillary malformations, venous malformations and lymphatic malformations. Different combinations of malformations are quite common. In clinical practice malformations are classified as either low-flow or high-flow lesions. Malformations with arterial components are considered to be high-flow lesions. Capillary, venous, lymphatic malformations and their combinations are considered to be low-flow lesions [11, 17]. Hemangiomas are benign tumours in infancy. They demonstrate proliferation of endothelial cells at pathologic examination. Most hemangiomas are recognized clinically and subside spontaneously.

Various imaging modalities are needed in the diagnosis of vascular anomalies. The correct radiological diagnosis is essential in order to decide the most appropriate treatment for the patient. MRI is an excellent modality for differentiating hemangioma from vascular malformations and in defining the extent of vascular anomalies and their relationships to adjacent structures [18]. Venous malformations may be difficult to differentiate from lymphatic malformations on MRI, but contrast-enhanced images improve the accuracy of the diagnosis (Fig. 1) [19]. Color Doppler ultrasound is helpful when imaging the different vascular characteristics in mixed vascular malformations. Color Doppler ultrasound also differentiates hemangiomas from vascular malformations [20]. Ultrasound generally identifies lymphangiomas, because there is no flow in Doppler. However, lymphangiomas may not be distinguishable from venous malformations [11].

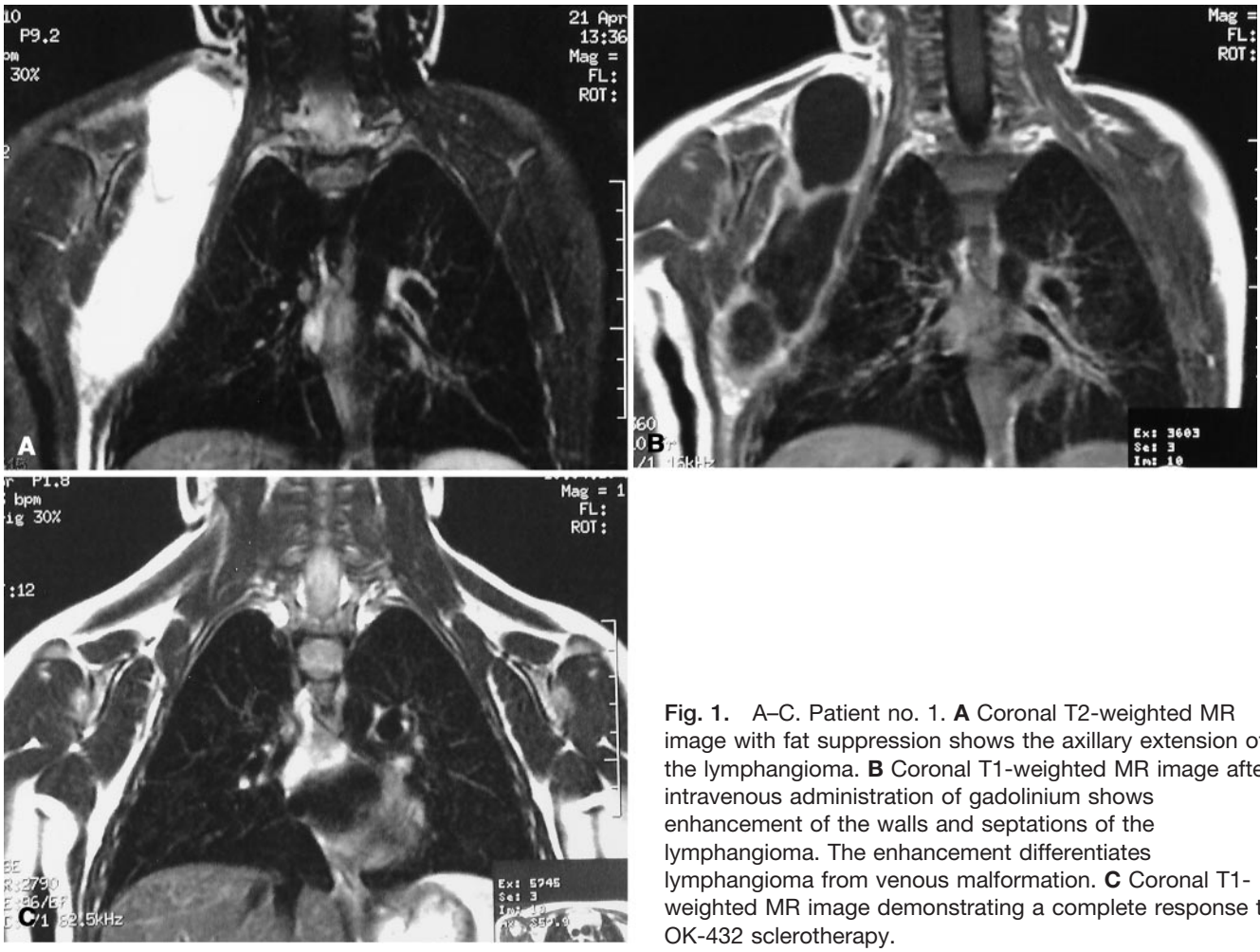

Fig. 1. A–C. Patient no. 1. **A** Coronal T2-weighted MR image with fat suppression shows the axillary extension of the lymphangioma. **B** Coronal T1-weighted MR image after intravenous administration of gadolinium shows enhancement of the walls and septations of the lymphangioma. The enhancement differentiates lymphangioma from venous malformation. **C** Coronal T1-weighted MR image demonstrating a complete response to OK-432 sclerotherapy.

Spontaneous regression of lymphangiomas is rare. Although they are benign lesions, their treatment is justified because of the complications they may cause when rapidly increasing in size. The most widely accepted therapy has been surgery, with preservation of the neural and vascular structure involved. When resection is complete, there is a low recurrence rate. This is possible in only 18–50% of cases [7]. Incomplete resection and multiple surgical interventions are expected in the case of a large and infiltrating tumor. Problems with surgical treatment include the possibility of scarring and damage to surrounding structures. When resection is incomplete, residual cysts may grow, leading to significant recurrence in one third of children [7]. Nonsurgical treatment with diathermy and radiation therapy has been attempted [10]. Intralesional injection of various sclerosing agents such as alcohol, boiling water and bleomycin has been used for treatment with good reduction of lymphangiomas [7, 10, 11]. However, these agents may spread outside the thin-walled lesion and cause damage to the surrounding structures, making subsequent surgery difficult and involving extensive scarring. Bleomycin is known rarely to cause pulmonary fibrosis [21]. Due to their limitations the use of sclerosing agents has met with only limited success.

Lymphangiomas are rare, and gathering sufficient numbers of patients to gain enough experience and reliable information on the new treatment option is problematic. Greinwald et al. [10] reported 1999 treatment of 12 lymphangioma patients with OK-432. Radiographic evaluation showed that six patients had macrocystic lesions, three had microcystic lesions and three had mixed lesions. Five of 12 patients (42%) evinced a complete or substantial response to OK-432 sclerotherapy. Macrocystic lesions showed the best response to therapy. There were no significant complications. Ogita et al. [14] have published the largest report of OK-432 treated patients so far. In 1994 Ogita reported his results from treatment of 64 lymphangioma patients. In this study 90% of the macrocystic lesions and 50% of the microcystic lesions showed a complete or marked shrinkage. There were no significant complications or scarring. Our results concur with previous reports [7, 12, 15, 16, 22]. Eleven of 14 patients (79%) had complete or marked shrinkage; seven of these were macrocystic lesions. All but one (No. 9) of the patients responded to therapy. The only

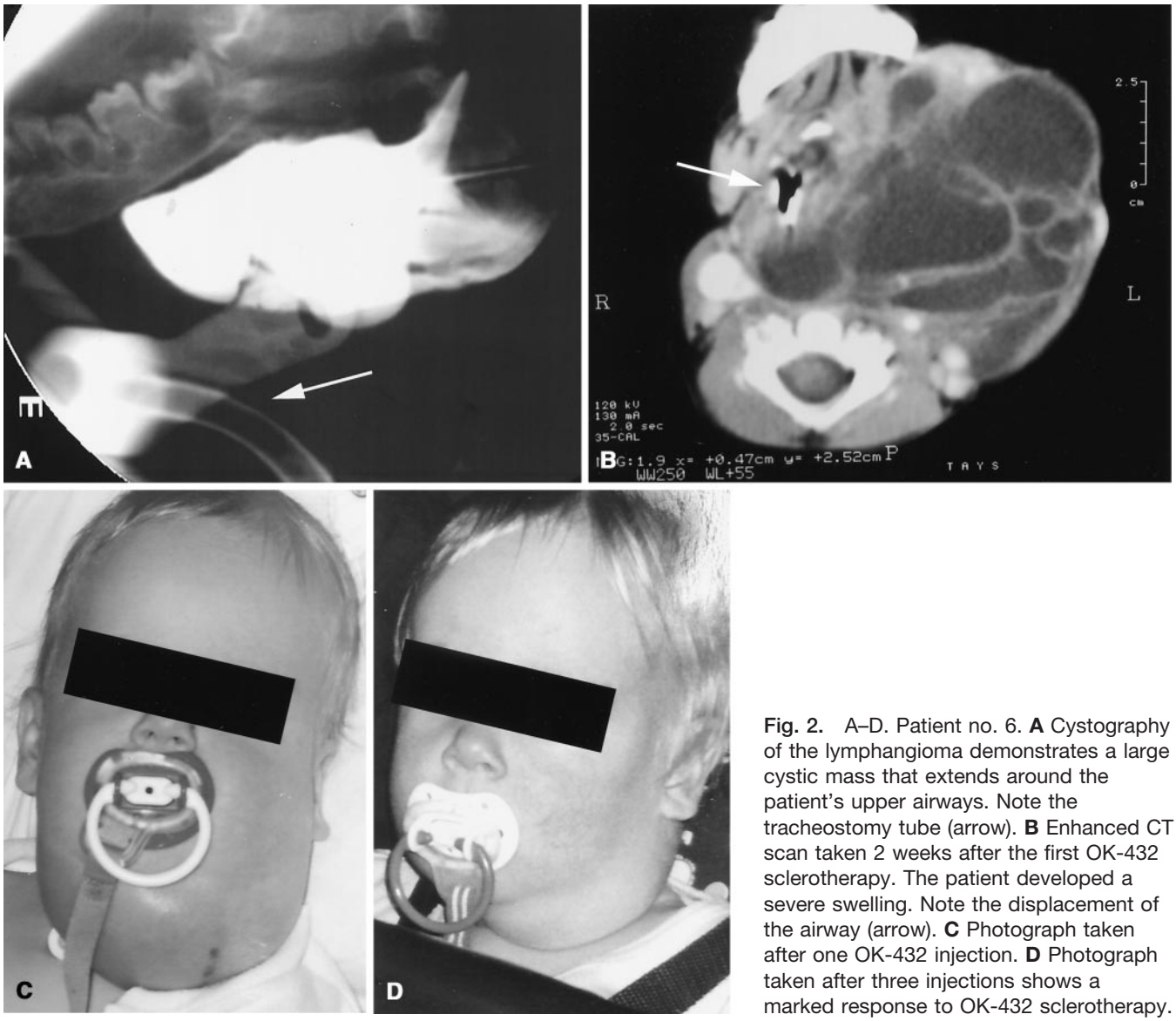

Fig. 2. A–D. Patient no. 6. **A** Cystography of the lymphangioma demonstrates a large cystic mass that extends around the patient's upper airways. Note the tracheostomy tube (arrow). **B** Enhanced CT scan taken 2 weeks after the first OK-432 sclerotherapy. The patient developed a severe swelling. Note the displacement of the airway (arrow). **C** Photograph taken after one OK-432 injection. **D** Photograph taken after three injections shows a marked response to OK-432 sclerotherapy.

common side-effect of OK-432 injection is a slight fever for a few days after the therapy. On the other hand this is an expected reaction to a successful injection.

The head and neck region is the most frequently affected site and in this area, including especially the airways, great vessels and eyes, there may appear particular and unexpected serious reactions during treatment sessions and thereafter. Depending on the location of the lesion it might be advisable to have a possibility for intensive care. Teamwork with experienced radiologists and clinicians is therefore of great importance to anticipate the possible side-effects and complications and to be able to take deal with them in time. The only potentially serious side-effect in our study population was upper airway compression due to acute swelling of lymphangioma after OK-432 injection in patient no. 6. The patient's airways were ensured with tracheotomy in the first two treatment sessions, but not in the interval, when the swelling occurred (Fig. 2).

Those patients who had complete or marked regression in their lesions were treated with OK-432 as first-line treatment. Those patients who had previously undergone surgical resection or received some other treatment responded only with marked or moderate regression following OK-432 therapy in our study population, in spite of a larger number of treatment sessions and greater volumes of OK-432 (Table 2). In the light of our limited results OK-432 injections should perhaps be the first treatment in complicated cases. In non-radical surgery there is a high recurrence rate. However, recurrence of disease after OK-432 therapy is unusual, although long-term results are lacking. In our series the mean follow-up time was 1 year 8 months after the first injection (range 9 months to 2 years 10 months). So far there have been no recurrences.

In summary, there is no evidence of serious side-effects so far; the only sedation needed for adults is local anesthesia. Macrocystic lesions tend to have the best outcome and there

are far fewer recurrences compared with other treatment options. There have also been no reports on scarring of the surrounding tissue and structures or disturbances in function. These facts encourage us to continue with OK-432 treatment trials. The treatment of lymphangiomas is challenging: centralization of treatment and fluent teamwork between radiologists and clinicians is necessary to collate all the experience from treatment to benefit this small group of patients.

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