SWISS SOCIETY OF NEONATOLOGY

Winner of the Case of the Year Award 2006

Intralesional injection therapy with OK-432 (Picibanil®) in a full term infant with multi-cystic lymphangioma colli

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Lymphangiomas are congenital malformations of the lymphatic system originating during fetal development as a result of dysplastic sequestration of lymphatic tissue (1). They are present at birth in 50% of cases. The lesions consist of dilated endothelium-lined spaces that vary in size from microscopic channels (cavernous lymphangioma) to large cysts (cystic lymphangioma or cystic hygroma). Although histologically benign, these lesions may expand into surrounding tissues or vital structures similar to malignancies, sometimes causing life-threatening complications (2). Cystic lymphangiomas commonly appear in the neck (75%) and axillary region (20%), whereas cavernous lymphangiomas show a predilection for the tongue, cheek, thorax, extremities and retroperitoneal area (3).

Complete surgical excision is the treatment of choice. However, total excision with preservation of involved vital structures is not always possible without serious complications. Incomplete excision is frequently associated with recurrence. Alternatively, various sclerosants have been used, but the results have not been satisfactory. In 1987 Shuhei Ogita et al. from the Childrens's Research Hospital in Kyoto, Japan, showed in a case study of a cystic hygroma that intracystic injection of OK-432 (Picibanil®, Chugai Pharmaceutical Co, Tokyo, Japan) lead to total shrinkage of the lesion without any side effects or cosmetic problems (4). OK-432 (Picibanil®) is a lyophilized incu-

Fig. 1

Appearance of lymphangioma colli at the age of three weeks.

bation mixture of the low virulent Su strain of Group A Streptococcus pyogenes of human origin which has lost its streptolysin S-producing ability and penicillin G potassium (5). In Japan, OK-432 has been used as a biological response modifier, mainly in the treatment of alimentary tract cancer, lung cancer, head and neck cancer and thyroid cancer with no serious adverse effects.

We describe the use of this non-operative treatment in a newborn with an extensive multicystic lymhangioma colli.

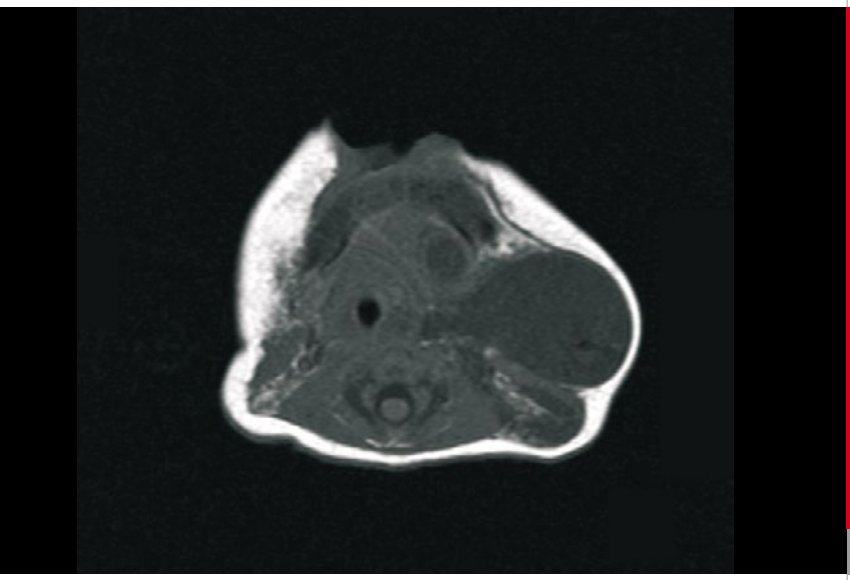


Fig. 2

MRI: T1-weighted axial image of neck.

We report on a full term male neonate who was born by primary caesarean section in an outside hospital and was transferred to our neonatal intensive care unit right after birth because of a large, soft, fluctuating mass on the left side of the neck (Fig. 1). Postnatal adaptation was uncomplicated with Apgar Scores of 9, 10, 10 at 1, 5 and 10 minutes, respectively. The boy's birth weight was 3320 g and he was in no apparent distress. The mother was a healthy 31-year-old G2/P2 with a normal family history. We performed an ultrasound examination of the mass as well as an MRI which revealed an extensive multicystic lymphangioma extending from the floor of the mouth over the left

Fig. 3

MRI: T2-weighted axial image of the neck.

cervical and nuchal region to the aortic arch and the origin of the left subclavian artery (Fig. 2-5, movies 1-2). There were no other anomalies.

The postnatal period was uneventful without feeding problems and absence of respiratory distress.

At the age of 2 months, we started therapy with OK-432 instillation under general anesthesia. First, we aspirated intracystic fluid from the main cervical cyst under ultrasonographic guidance and then we injected 20 ml of OK-432 solution at a concentration of 0.01 mg/ml into the cyst lumen to the maximum dose of

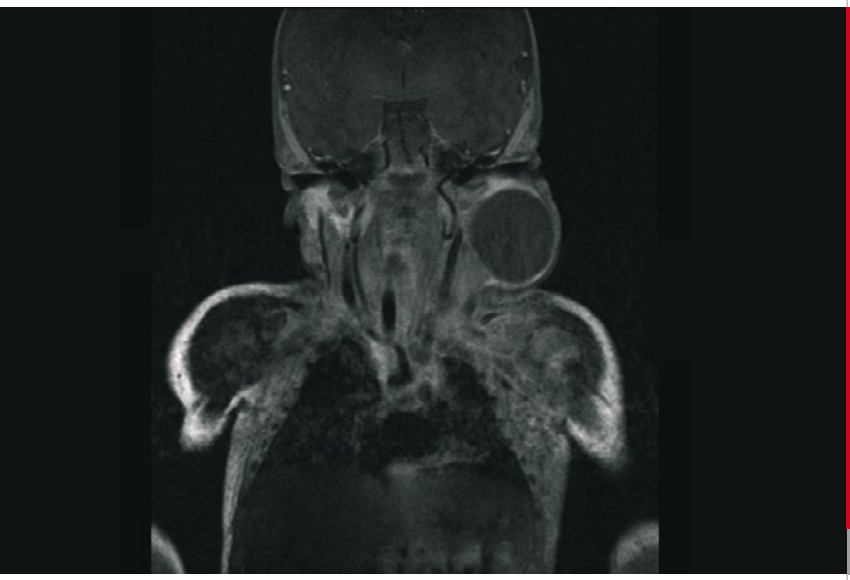


Fig. 4

MRI: T1-weighted coronal view of neck and chest.

0.2 mg (20 ml) per injection. As expected, a few days after the first injection the boy developed a localized inflammatory reaction and a low grade fever which responded well to antipyretics. After one week, the main cyst had filled up again so that we repeated the procedure and injected again 20 ml (0.2 mg) of OK-432 solution. After the second injection, the systemic and localized inflammatory response was less pronounced, but the boy developed moderate and transient thrombocytosis. At the age of 3 months, the main cervical cyst was clearly reduced in size so that two other main cysts which were located in the nuchal and submental regions were

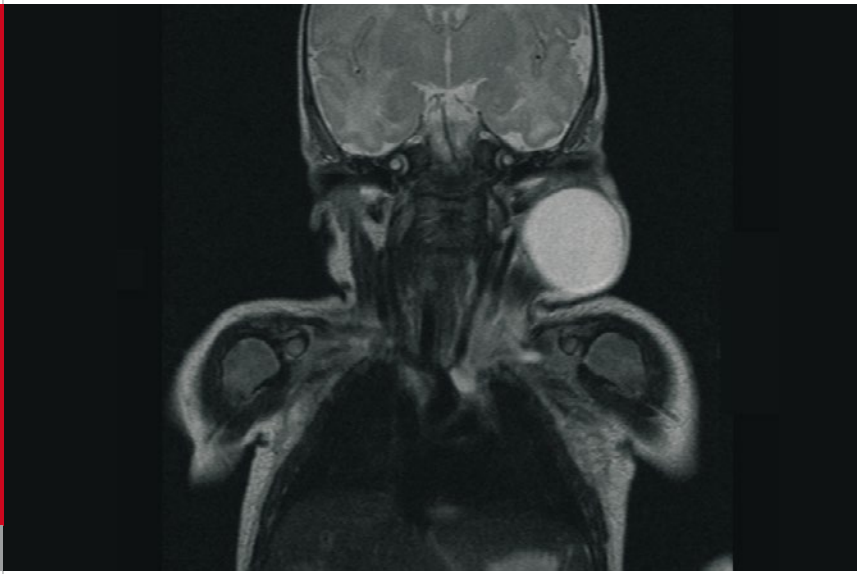


Fig. 5

MRI: T2-weighted coronal viewof neck and chest.

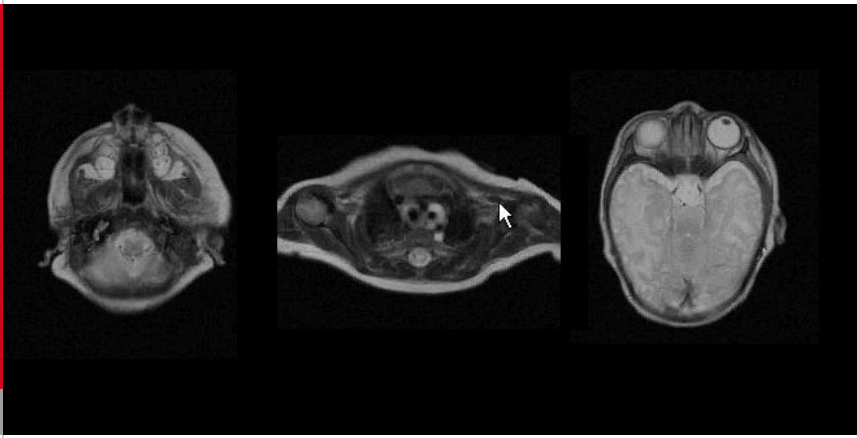
also treated with aspiration and instillation of 20 ml OK-432 solution under general anesthesia. On a clinical examination at the age of 4 months (after 4 instillations of OK-432 solution) into the different cysts, the cervical cyst had involuted almost entirely and the nuchal cyst was greatly reduced in size. At the age of 5 months, we repeated the aspiration and instillation of OK-432 solution into the nuchal cyst. At the age of 7, 12 and 19 months (Fig. 6), complete resolution of the cystic lymphangioma was observed. The boy was thriving and developing normally.

Fig. 6

Patient at the age of 19 months.

DISCUSSION

Because of the extent of the lymphangioma and its vicinity to vital structures, we decided to use a non-operative approach in our patient. The literature suggests that intralesional OK-432 instillation is currently the most appropriate treatment of unresectable lymphangiomas (2, 3, 6, 8, 9). Macrocystic lesions show the best response to therapy (8, 10). The results are even better when OK-432 instillation is used as a first-line therapy. Ogita et al. reported distinct or complete shrinkage of the lesion without serious side effects in 92% of cases (2). Banieghbal et al. found complete regression of cystic lymphangiomas in 95% of cases (7). Hall et al. (11) reported that lesions located in the



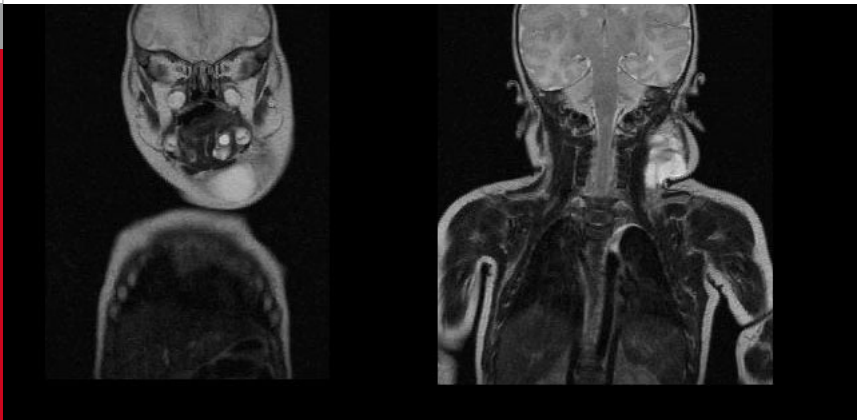
Movie 1

MRI: serial axial T2 images.

Note: movies can be accessed at www.neonet.ch/case-2006-04

MRI: serial coronal T2 images.

Movie 2



head and neck regions measuring less than 5 cm in diameter responded best to the instillation therapy.

The therapeutic effect of OK-432 is a local inflammatory reaction with infiltration of neutrophils and macrophages into the cystic spaces and extensive production of various cytokines and other inflammation mediators. These reactions increase endothelial permeability and accelerate lymphatic drainage and shrinkage of the cystic spaces without any scar formation of the overlying skin (12, 13). Adverse reactions are mild and are present in 98% of treated patients. They include swelling and redness (85% of treated cases), transient low-grade fever (84%), and pain (14%). The major abnormal laboratory findings after instillation of OK-432 are increased white blood cell counts (64% of cases), increased CRP levels (72%) and thrombocytosis (8%) (14).

OK-432 (Picibanil®) can be ordered at Chugai Pharmaceutical Co, Tokyo, Japan. Information about Dr. Shuhei Ogita can be obtained from his website or by contacting him by e-mail.

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