Sclerotherapy for Cavernous lymphangioma: Convenience of Early treatment

MC. Augustín-Morales, A. Molina-Carballo, J. Uberos, F. Contreras-Chova, A. Muñoz-Hoyos.

Departamento de Pediatría. Hospital Clínico San Cecilio. Granada. España.

RESUMEN

Los Linfangiomas son malformaciones vasculares congénitas constituidas por dilataciones quísticas de los vasos linfáticos delimitados por una línea de células endoteliales, que varían en tamaño desde canales microcópicos (linfangioma cavernoso) hasta grandes quistes (higroma quístico). Puede hacerse un diagnóstico prenatal de grandes lesiones quísticas mediante estudio ecográfico. A pesar de ser tumoraciones benignas, pueden ejercer compresión de estructuras vecinas y la capa endotelial que delimita los quistes es vulnerable a agentes infecciosos o químicos. Con vistas a evitar las complicaciones de la cirugía, se han ensayado distintas sustancias esclerosantes para tratar los linfangiomas. Exponemos la experiencia de un caso tratado con éxito con una dosis única de OK-432 (picibanil), un extracto liofilizado obtenido de la incubación del estreptococo pyogenes grupo A, seguido de la escisión quirúrgica de los restos del linfangioma. Además, brevemente revisamos los conocimientos actuales acerca de este tipo de malformaciones congénitas.

Palabras clave: *Malformaciones vasculares. Linfangioma. Tratamiento esclerosante. OK-432.*

ABSTRACT

Lymphangiomas are congenital vascular malformations constituted by cystic enlargement of the lymphatic vessels delimited by a layer of endothelial cells that vary in size from microscopic channels (cavernous lymphangioma) to large cysts (cystic hygroma). In the prenatal period, the diagnosis can be done by ultrasound scan. Even in benign tumours, they can exert compression of neighbouring structures and the endothelial layer that delimits the cysts is vulnerable to infectious or chemical agents. With the aims to avoid the surgery complications, different chemical substances have been employed to produce sclerosis of the lymphangioma. This paper reports a case of cavernous lymphangioma that was associated with an repeated infectious complication. Finally, it was treated with success by an unique dose of OK-432 (picibanil), a lyophilized mixture of Streptococcus pyogenes group A of human origin, followed by the surgical excision of the remainders of the lymphangioma. Moreover, we make a brief review of the current knowledge on this type of congenital malformations.

Keywords: *Vascular malformations. Lymphangioma. Sclerotherapy. OK-432.*

INTRODUCTION

Lymphangiomas are congenital vascular malformations constituted by cystic enlargement of the lymphatic vessels (1). They represent a 6% of benign tumours at paediatric age being detected between

65% and 75% at the time of birth and until a 90% at the end of second year. Histologically, they can be grouped in cystic hygroma, cavernous lymphangioma and mixed one. The lesions are delimited by a layer of dilated endothelial cells, which differ in size from microscopic channels (cavernous lymphangioma) to large cysts (cystic hygroma). Prenatal diagnosis of big cystic injuries can be achieved by ecographic studies at the end of the first trimester (2). The most common location of lymphangioma is the head with predominance of cystic forms, and especially the neck with a 90%, maybe this is consequence of the complexity of the lymphatic cervical system. Other typical locations are in armpit, thorax, mediastinal area, retroperitoneal, buttocks and anus-genital region, with predominance of the cavernous forms. The location of these being tumours is important because they can produce compression of vascular and nervous structures, as well as of the respiratory tract. Additionally, the endothelial cell layer that delimits the cysts is vulnerable to infectious or chemical agents. Occasionally, the infection can provoke the spontaneous reduction of the size of some cysts, but this is not very frequent. The convenience of an early treatment by the injection of different sclerosant substances is recommended because lymphangiomas have high predisposition to be infected and to avoid the complications of the surgery (3). This report describes the success obtained in a patient with a huge cavernous lymphagioma treated only with one dose of OK-432 (picibanil). This treatment provoked a very significant reduction of lymphagioma which allowed the surgical excision of the remained lymphangioma.

CLINICAL CASE

Neonatal male born to term of childbirth for caesarean for not progression, after a normal and controlled pregnancy. During the clinical examination, it was observed a larger tumefaction, located between nipple and left armpit with a soft consistency but without changes of the skin coloration (Fig.1 panel A). The other physical explorations were compatible with the normality. Then, the Department of Infantile Surgery accomplished an ultrasound scan and diagnosed that this tumefaction was a cavernous lymphangioma with a size of 9 x 6 x 2 cm. The surgery service decided to adopt a conservative conduct based in three reasons: the clinical normality of the patient; the location of the lymphagioma had a low theoretical rate of complications; and, the difficulty of the complete exeresis of the tumefaction due to its great size.

With 3 months old, the patient initiated a clinical symptom of high fever, higher to 39ºC, without an apparent focus but with a normal physical exploration and normal urine sediment. Few hours later, a second physical evaluation revealed a tenuous red line through the tumefaction that later increased in size. Therefore, the patient was hospitalized and initiated an antibiotic intravenous treatment. Among other clinical analyses, it is important to point out the haemogram showed leucocytes and left deviation and both hemocultive and serologic analyses were negatives. Two weeks later, the symptoms reappeared and it was necessary a new antibiotic treatment.

In these circumstances, the parents decided to ask a second opinion after knowing the possibility of an alternative treatment without surgery that it was developed in Japan and it is designed as OK-432 or picibanil. Thus, the parents made the decision to travel to Japan (mother was Japanese), specifically to the Osaka Medical Center and Research Institute for Maternal and Child Health to initiate this alternative treatment. There, a new echography examination revealed a bright zone among the cysts that they could be a consequence of the infection process. Then, it was made a punction of

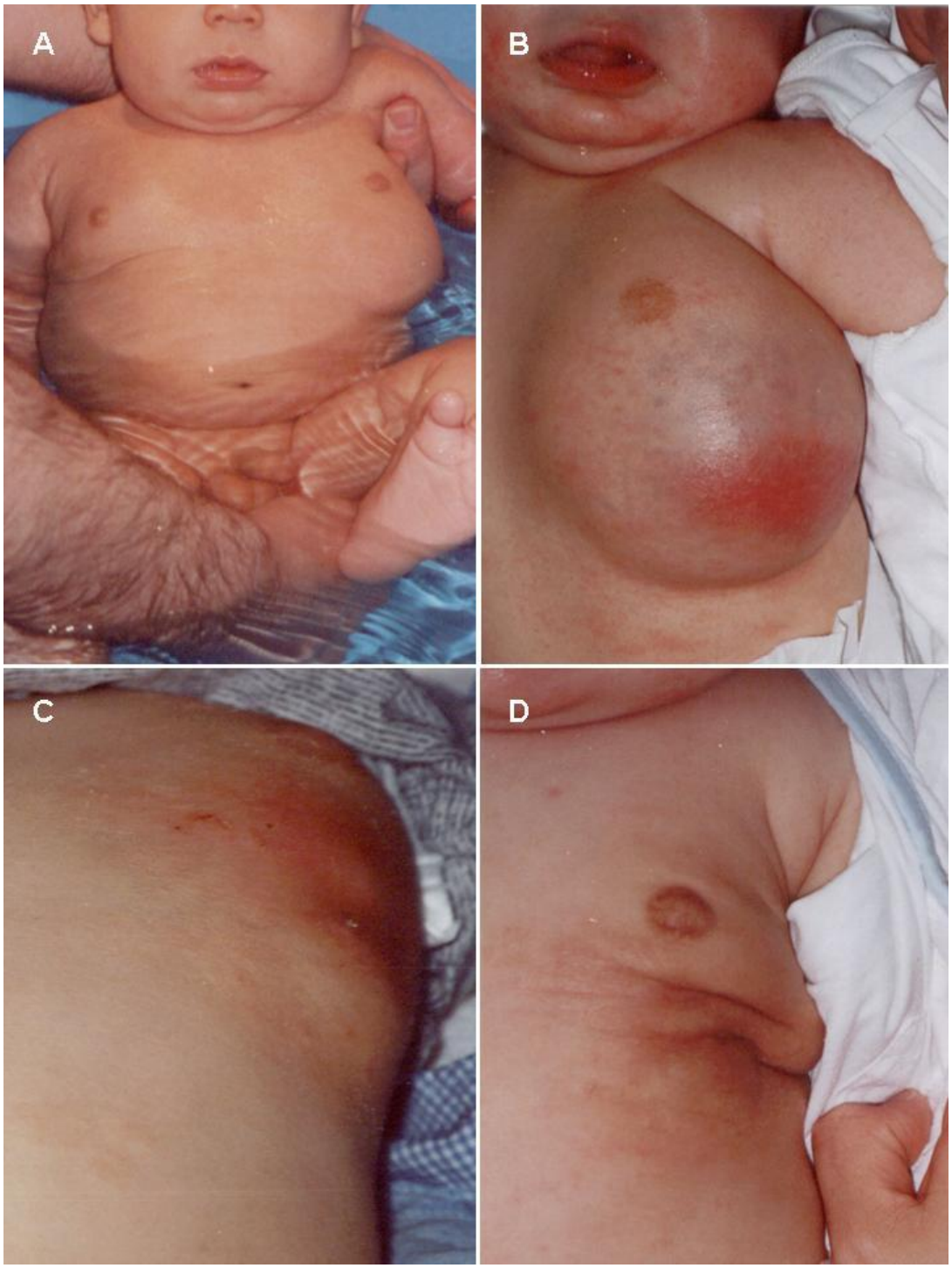

Figure 1. *Appearance of cavernous lymphangioma before and after picibanil treatment and surgery. Panel A, appearance of lymphangioma at 4th month after bird. Panel B. Appearance one day after the second dose of picibanil which was stopped follow by an antibiotic treatment during 5 days. Panel C, appearance at 10th day of antibiotic treatment. Panel D, appearance one day before surgery to eliminate the lymphangioma.*

the inflamed zone to obtain the lymphatic content for microbiological analysis.

With 4 months old, it was programmed the administration of four intratumoral infiltration with picibanil with an interval of one month for each injection.

Table 1. Classification of congenital vascular lesions according to Mulliken & Glowacki and modified by Waner & Sue.

HAEMANGIOMAS
VASCULAR MALFORMATIONS
Capillaries
Venulares
Venouses
Lymphatic
Arteriovenouses
Mixed
Venolymphatic
Venous-venular

Next day of the first infiltration, the patient showed a fever of 38ºC which disappeared 24 h later.

One day before of the second injection, the patient showed again high fever. He had also leukocytosis with left deviation and high PCR. Therefore, the initial protocol was postponed. In this moment the lymphangioma showed a large tumefaction and turned red (Fig. 1, panel B). The patient was hospitalized and initiated again an antibiotic treatment for 5 days. After 4 more days, the tumefaction started to diminish considerably (Fig. 1, panel C) and the patient was discharged from the hospital. Later the lymphangioma continued diminishing.

With 8 months old, the surgery was programmed to eliminate the remained lymphangioma. Figure 1, panel D showed the aspect of the lymphangioma one day before of the surgery. As a consequence of the location it was necessary the elimination of a portion of the pectoral muscle. The histological analysis of the extirpated sample showed that some small portion of the lymphagioma remained. The drainage was removed 4 days later and the patient continued in the hospital during 10 more days for antibiotic treatment. Two years later, the clinical revision showed an asymptomatic patient.

DISCUSSION

The vascular anomalies are grouped in tumours and malformations. In the first group, the most frequent vascular anomalies are the haemangiomas which represent until a 12% of the neonates being more frequent in girls. Usually, these tumours are not present in the birth and their growth is due to hyperplasia during the 10-12 months of age. Then, the haemangiomas suffer a regression which can take between 10 to 12 years. On the other hand, the vascular malformations affect lower percentage of neonates, approximately a 1.5%, that the haemangiomas. These vascular malformations are always present in the birth, usually they grow up for hypertrophy and sometimes in relation with traumatism, infectious processes, hormonal changes, etc, and they never suffer involution. A 66% are of the venous type, without differences for sex or racial group (4). The vascular malformations are errors of the embryological development which can have a diffuse or specific localization. It has been described some random mutations with a potential familiar hereditary character, as well as disorders of the neurological vascular modulation. Table 1 shows the classification of the malformations venulares and arteriovenouses according to Mulliken & Glowacki.

Among the vascular lymphatic malformations, the most frequent are the vascular malformations. Traditionally, they have considered and treated as two different (1,5), without considering the embryological common origin: the truncular form (which includes the primary congenital lymphedema that it can be early or tardive types depending on the moment of appearance)(6) and the extratruncular form (lymphangioma, cystic higroma circumscribed lymphangioma and

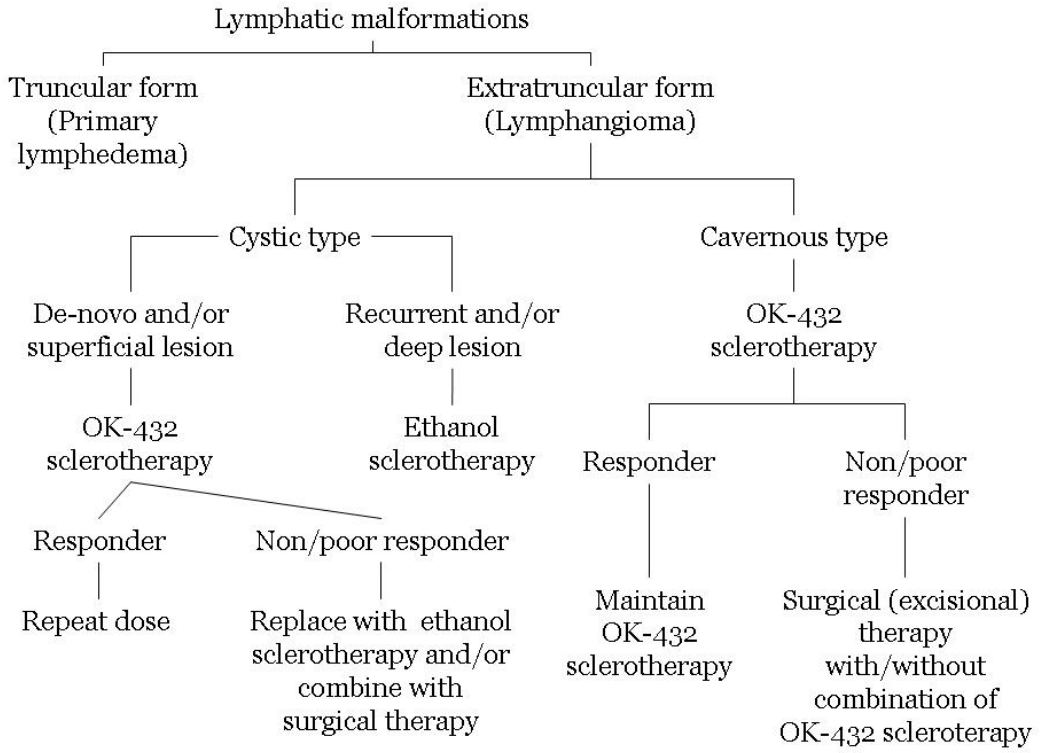

Figure 2. *Algorithm for the evaluation and treatment for the extratruncular lymphatic malformations modified by Lee et al. (1).*

lymphangiomatosis). They have been treated in an independent way. The lymphangioma is a remnant of the embryonic lymphatic system that it remains after the birth, once his development is stopped in an initial stage of the embryogenesis, but that retains the potential evolutionary of the mesenquimal cells. The lymphatic vessels, constituted by a layer of endothelial cells, appear dilated as cysts that contain lymph and that are delimited by conjunctive tissue. The extratruncular form of the lymphangioma is less serious than other forms of congenital vascular malformations such as the venous malformations or arteriovenouses, except that it is located in a vital region or provokes a serious functional or cosmetic disorder.

The clinical aspect changes depending on the size, depth and location of the injury, being frequent the presence of multiple translucent vesicles which have a viscous content at cutaneous or mucous level. The superficial injuries can be connected to deeper lymphatic cisterns, to subcutaneous or submucous level. The surrounding skin is normal and sometimes with a bluish tonality. It is frequent that the slight injuries remain silences during more time, and can be exacerbated by an accidental or surgical traumatism, a intralesional haemorrhage (8%), an infection (sepsis, up to 16% of cases) or a hormonal change. For extension, the cervical injuries can compress the pharynx and/or compromise the respiratory conducts (7). The near ones to the orbit can produce protopsis.

The deep injuries produce skeletal hypertrophy in the majority of cases. This hypertrophy can not be explained like in other vascular malformations for an increase in the blood irrigation. The

hypertrophy in the jaw can cause prognathism and a bad occlusion. The anomalies to the lymphatic thoracic level, especially of the thoracic conduit, can produce respiratory distress for accumulation of lymph in the intrapleural cavity (chylothorax). In the gastrointestinal tract, they can cause hipoalbuminemia due to the loss of protein by enteropathy. In an extremity, the big lymphatic malformations often produce pain, inflammation and gigantism at the expense of growth of skeletal muscle (1). The pelvic injuries can be revealed for urinary obstruction, diarrhoea and recurrent infections. Gorham-Stout syndrome, or disappearing bone disease, is due to a progressive osteolysis induced by a lymphatic malformation on soft tissues and skeleton (8).

There have been described some cases of regression of the vascular lymphatic malformations, probably due to the appearance of a lymphatic-venous shunt after sometime, though many injuries "involutionated". In fact, they could be subcutaneous haemangioma that follow it natural evolution.

The OK-432 (Picibanil; Chugai Pharmaceutical Co., Tokyo, Japan) is a lyophilized mixture of the *Streptococcus haemolytic* type III (pyogenes) from the Group A, that after being incubated with penicillin G has lost the contagiousness and the capacity of synthesis of fatty acids, proteins and nucleic acids, as well as the production of streptolysin O and S. Although it supports that they keep the capacity to consume glucose and their enzymatic properties. The first report about it usefulness was in 1987 in Japan (9). The picibanil had been used as modifier of the biological response in the treatment of tumours (5,10,11), fundamentally in digestive, pulmonary, cranium and neck, without any remarkable adverse effects. It has been also used in the local treatment of the atopic dermatitis (12), ganglions (13) and the moluscum contagiosum in immunodepressed patients (14).

The physiopathological mechanism of the OK-432 is based in the capacity to induce and keep activated the inflammatory cascade with an increase of white cells and cytokines, mainly IL-6 (a multipowerful cytokine) and IL-8 (inducer of macrophages). Before treatment, the majority of the cellular content of the intracystic liquid are lymphocytes, whereas 24 hours later it increases the number of white cells, neutrophils with a 72% and macrophages with a 21%. At fourth day, a 72% of the cells are again lymphocytes. The activity of the tumour necrosis factor (TNF) and IL-6 increases immediately after the injection, and remains elevated even in the fourth day (15). By cytometry of flow of monoclonal antibodies, it has been demonstrated an increase of the natural killer cells (CD56+) and the T cells (CD3+) which induce the cytotoxicity on the endothelial cells of the lymphangioma. This provokes the subsequent increase of IL-12, TNF-alpha and interferon-gamma, as well as the vascular endothelial growth factor and it soluble receptor (11,16). The increase of these inflammatory mediators explains usual fever and tumefaction that they persist between 1 to 3 days after the injection. The increase level of white cells and cytokines (including the TNF) by the administration of OK-432 suggest that these factors enhance the endothelial permeability and accelerates the lymphatic drainage until the collapse of the cysts is produced (15). It is considered that the mononuclear cells cannot keep activated in the absence of OK-432, which disappears from the cysts in one week, together with the cytotoxicity induced by the immunocompetents cells.

The OK-432 usually is applied after 3-4 months of the birth, though it has been also administered in newborn children. Before the treatment, it must be measured the size of the injury, take pictures and perform an ecography exploration (3).

Although it is not a usual exploration, the magnetic resonance allows to visualize the lymph and define the range of infiltration, whereas the lymphography would allow to demonstrate the intercommunication among the cysts.

The OK-432 is supply as lyophilized powder of 0.1 or 0.5 mg (http://www.asahi-net.or.jp/~VF6S-OGT/). It is diluted in physiological serum to obtain a concentration of 0.1 KE/ml. It is administrated with a local anaesthesia but previously it proceed to the aspiration of the cyst content that it is replaced by a equal volume of the diluted OK-432. It has been established a maximum of 20 ml per injection (0.2 mg) although it has been obtained a bigger volume of cyst content. It can be applied a half diluted concentration (0.05 KE/ml) mainly in newborn children. The painful zones are infiltrated with 3 ml of 0.5% lidocaine plus 2 ml of physiological serum. After the injection, it could be necessary to pay attention to a potential hypersensitivity reaction, although it has not been described any case of serious complications. The habitual secondary effects are fever of 38-39ºC (79% of cases), approximately six hours after the injection for 2-3 days, reddishness (92%), tumefaction and pain to palpation (17). Usually, during the first month, the injury does not change in size. Then, it begins to reduce the size quickly even it can disappear completely. The beginning of this reduction can be delayed until to 6 weeks, therefore the interval between injections must be 5 to 6 weeks, though if the first dose does not provoke any type of local reaction, it is possible to inject again a week later. To get the maximum reduction, before considering the surgery, can be required up to 5-6 injections, especially in the cavernous and mixed types because they contain a major proportion of connective tissues. In order that sclerotherapy can be efficient, the treatment with OK-432 must be the first option since the post-surgical cicatrisation interrupts the necessary intercommunication of the cysts (16).

In the case of the extratruncular lymphangiomas which are less critical, the conservative treatment has been accepted as alternative to the surgery even when there is probability of infection and sepsis. At present, the OK-432 is the preferred treatment in the macrocystic lymphangiomas with a rate of success up to 96% (18) or when the surgical methods are not possible for their location, extension or morphologic characteristics (19). For other authors, the surgery continues being the best alternative of treatment, especially if the respiratory tract is compromised, postulating that the sclerosant substances are reserved for persistent lymphangiomas or recidive tumour already operated (20). The residual post- surgical sclerosis can avoid the intercyst flow of the sclerosant substances and reduce their efficiency. In the opposite way, the sclerosant substance can induce fibrosis on adjacent structures and this might impede the surgical complete exeresis with an increase of recurrences, although this possibility is not usually reported.

In the case of venous malformations, the multidisciplinary teams use pure ethanol (in combination or no with other substances that cause embolization) to reduce the morbidity and recurrence (1). The reason is that ethanol has the capacity to destroy permanently the endothelial cells minimizing the probability of recurrence, though it can provoke progressive fibrosis with the subsequent contraction of the affected muscles. Figure 2 shows the therapeutic algorithm used for the evaluation and treatment of the extratruncular lymphatic malformations (1).

In summary, the report of this clinical case allow us to make a brief review of lymphangiomas directed to primary care pediatricians and to point out the

convenience of the early treatment of this type of vascular malformations to avoid the high probability of complications by infections and to remember the usefulness of the sclerosant substances such as the OK-432 (picibanil) even in microcystic lymphangiomas (cavernous) of great size which are not localized on the head and neck

REFERENCES

1. Lee BB, Kim YW, Seo JM *et al.* Current concepts in lymphatic malformation. *Vasc. Endovascular. Surg.* 2005; 39: 67-81.

2. Suzuki N, Tsuchida Y, Takahashi A *et al.* Prenatally diagnosed cystic lymphangioma in infants. *J. Pediatr. Surg.* 1998; 33: 1599-1604.

3. Redondo P, Fernandez M. Protocolo de actuación ante hemangiomas y/o malformaciones vasculares. *An. Sist. Sanit. Navar.* 2004; 27 Suppl 1:133-40.: 133-140.

4. Redondo P. Clasificación de las anomalías vasculares (tumores y malformaciones). Características clínicas e historia natural. *An. Sist. Sanit. Navar.* 2004; 27 Suppl 1:9-25.: 9-25.

5. Kurokawa T, Hattori T, Furue H. Clinical experiences with the streptococcal anticancer preparation, OK-432 (NSC-B116209). *Cancer Chemother. Rep.* 1972; 56: 211-220.

6. Chen M, Chen CP, Shih JC *et al.* Antenatal treatment of chylothorax and cystic hygroma with OK-432 in nonimmune hydrops fetalis. *Fetal Diagn. Ther.* 2005; 20: 309-315.

7. Giguere CM, Bauman NM, Smith RJ. New treatment options for lymphangioma in infants and children. *Ann. Otol. Rhinol. Laryngol.* 2002; 111: 1066-1075.

8. Ogita S, Deguchi E, Tokiwa K, Iwata J, Kubota Y, Iwai N. Ongoing osteolysis in patients with lymphangioma. *J. Pediatr. Surg.* 1998; 33: 45-48.

9. Ogita S, Tsuto T, Tokiwa K, Takahashi T. Intracystic injection of OK-432: a new sclerosing therapy for cystic hygroma in children. *Br. J. Surg.* 1987; 74: 690-691.

10. Horii Y, Iino Y, Maemura M, Horiguchi J, Morishita Y. Inhibitory effects of OK-432 (Picibanil) on cellular proliferation and adhesive capacity of breast carcinoma cells. *Oncol. Rep.* 2005; 13: 289-294.

11. Katano M, Morisaki T. The past, the present and future of the OK-432 therapy for patients with malignant effusions. *Anticancer Res.* 1998; 18: 3917-3925.

12. Horiuchi Y. Topical streptococcal preparation, OK-432, for atopic dermatitis. *J. Dermatolog. Treat.* 2005; 16: 117-120.

13. Taniguchi T, Motomura H, Ohba N, Harada T, Muraoka M, Ishii M. Clinical results of OK-432 injection therapy for ganglions. *J. Dermatol.* 2005; 32: 262-265.

14. Inui S, Asada H, Yoshikawa K. Successful treatment of molluscum contagiosum in the immunosuppressed adult with topical injection of streptococcal preparation OK-432. *J. Dermatol.* 1996; 23: 628-630.

15. Ogita S, Tsuto T, Nakamura K, Deguchi E, Tokiwa K, Iwai N. OK-432 therapy for lymphangioma in children: why and how does it work? *J. Pediatr. Surg.* 1996; 31: 477-480.

16. Fujino A, Moriya Y, Morikawa Y *et al.* A role of cytokines in OK-432 injection therapy for cystic lymphangioma: an approach to the mechanism. *J. Pediatr. Surg.* 2003; 38: 1806-1809.

17. Ogita S, Tsuto T, Nakamura K, Deguchi E, Iwai N. OK-432 therapy in 64 patients with lymphangioma. *J. Pediatr. Surg.* 1994; 29: 784-785.

18. Banieghbal B, Davies MR. Guidelines for the successful treatment of lymphangioma with OK-432. *Eur. J. Pediatr. Surg.* 2003; 13: 103-107.

19. Krainick-Strobel U, Kramer B, Walz-Mattmuller R *et al.* Massive cavernous lymphangioma of the breast and thoracic wall: case report and literature review. *Lymphology.* 2006; 39: 147-151.

20. Lee BB. Advanced management of congenital vascular malformations (CVM). *Int. Angiol.* 2002; 21: 209-213.