

## **TREATMENT OF GENERALIZED LYMPHANGIOMATOSIS WITH UKRAIN: A CASE REPORT**

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**Summary:** *We report on the first case of the use of Ukrain in the treatment of generalized lymphangiomas complicated with decubital ulcers in a child. Lymphangiomas presented in various parts of the body. Despite a highly unfavorable prognosis, the therapy with Ukrain proved to be of significant value, benefiting the general development of the young patient and ameliorating the course of the disease.*

### **Introduction**

Lymphangioma, or cystic hygroma, or lymphatic malformation, is a localized or generalized growth of anomalous lymphatic channels and cysts (1). These are relatively rare congenital malformations and make up approximately 6% of all benign lesions in children (2). Lymphatic anomalies occur in both sexes with equal frequency and in all races (3). Seventy to 90 percent are clinically evident at birth or become noticeable within the first two years of life (4). Lymphangiomas are usually found in the head and neck region. The axilla and mediastinum are the second most frequent location sites, and may be encountered as primary

sites or as the extension of a neck lymphangioma. The retroperitoneum and the extremities are rare sites for this tumor.

There are three main groups of lymphatic malformations. The first and most common group consists of hypoplasia or aplasia of lymph vessels and nodes leading to inadequate clearance and presenting as lymphedema. The second group consists of disorders of the circulation of chyle. The third group, presenting in our patient, consists of solitary or multiple cystic lymphatic malformations. Multicystic lymphatic malformations can be micro- or macrocystic (4). Transillumination is highly characteristic of macrocystic lymphangiomas (5).

The characteristic history of a lymphatic malformation is enlargement commensurate with the child's growth, with intermittent periods of swelling due to hemorrhage into the lesion.

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Lymphangiomas may cause marked disfigurement; recurrent infections; respiratory obstructions; malocclusion; and dysphagia, dysphonia and dysarthria, as a result of the infiltration and compression of neighboring structures.

Lymphangiomas may occur in association with venous malformation. Pure venous malformations can occur in any tissue in the body and can widely infiltrate skin, muscles, joints and, sometimes, bones. Combined lymphatic-venous lesions are often associated with skeletal elongation and hypertrophy. There was no evidence in our patient of bone involvement with the malformation, which was consistent with the main element being lymphatic.

We report on the treatment of generalized lymphangiomatosis in a child with the drug Ukrain. Lymphangiomas presented in various parts of the body and the course of the disease was unfavorable.

### **Case report**

The patient, S.D., male, was born on September 22, 1992, at 7 months of gestation, as the fourth child in a family. No congenital disorders had been observed previously in the family, and the mother subsequently gave birth to three more children without any congenital problems being observed.

A large soft tissue tumor on the left dorsal thorax wall was observed following delivery. A computed tomography (CT) scan carried out the day after delivery revealed a paravertebral lymphangioma in the left posterior mediastinum, and another in the area of the dorsal body wall. Clear communication between the tumors could not be seen on the CT. Both tumors were clearly separated from the spinal canal. A magnetic resonance imaging (MRI) scan performed on October 1, 1992, showed that the tumors were lymphangiomas, or cystic hygromas. The second paravertebral tumor had reached the arch of the aorta in the cranial direction.

During the first month of life, the swelling on the thoracic wall expanded and a skin infection occurred, following which the patient was admitted to the hospital. On admission, the patient was in good general condition, weight gain was adequate, and spontaneous motor activity was well developed. As before, there was a large, soft, fluctuating, brownish, blurred tumor.

On November 11, 1992, partial resection of the extrathoracic tumor was carried out. Under histological examination, lymphangiomatosis was verified and a residual tumor was confirmed. Wound healing proceeded very slowly and was complicated by relapsing infections treated with antibiotics.

An ultrasound examination carried out on April 20, 1993, revealed no free fluid in the abdomen and a small pleural effusion on the left side. Lymphangioma in the left inguinal area and bilateral scrotal hydrocele were diagnosed.

In June 1993, bilateral otitis media with purulent inflammation and perforation occurred and was treated with antibiotics.

A CT scan performed on November 9, 1993, revealed substantial growth of the existing tumors compared with September 1992, with partially intrathoracic and partially extrathoracic soft tissue tumors. The intrathoracic tumor surrounded the descending aorta and left clavicular artery. An MRI scan carried out on November 19, 1993, showed extended infiltration of the tumor into the spinal canal from Th1 to Th8, with maximum infiltration in Th4 to Th7; right upper dorsal lobar atelectasis was also revealed.

A CT scan performed on January 27, 1994, revealed clear extension of the extrathoracic tumor while the intrathoracic and spinal components remained unchanged. Neurological examination revealed an incomplete paraplegia, most likely L5-S1. Physical and neurosurgical examination revealed that due to the substantial tumor growth, the tumors were inoperable. Therapy with alpha-interferon (IFN)-2a (Roferon®-A3, Hoffmann-La Roche AG, Grenzach, Germany), 3

billion U/m<sup>2</sup>/day, s.c., was initiated. During IFN therapy, infections occurred frequently and were treated with antibiotics. Echocardiography revealed clear diminished left ventricular function, with the superior vena cava and vena azygos significantly dilated. Digitalis therapy with digoxin 0.125 mg p.o. (Lanicor®: Boehringer Mannheim, Mannheim, Germany) was initiated.

An ultrasound examination on March 8, 1994, revealed diffuse expansion of the tumor in the left thoracic area, and an MRI scan on April 8, 1994, showed no changes in the spinal canal.

Unfortunately, IFN therapy did not have any impact on the course of the disease and was discontinued after 4 months. No further therapy other than palliative care could be recommended by the physicians in charge of the case. The patient's general condition was extremely poor, since he could

neither speak nor move. He was discharged from the hospital to home care with a very unfavorable prognosis, with the parents being told that the child would never walk or speak.

In April 1995 therapy with Ukrain (Nowicky Pharma, Vienna, Austria) was started on an outpatient basis, initially at a dose of 10 mg, i.v., on alternate days, and later at 5 mg, i.v., twice a week. Informed consent of the parents was received before the start of therapy. A letter from the Drug Council of the Austrian Ministry of Health, Sport and Consumer Protection dated June 23, 1993, approved the use of Ukrain on an outpatient basis. The patient's state improved gradually.

On July 17, August 22 and September 19, 1995, three punctures of intra-abdominal cystic lymphangiomias were performed, with 3.5, 0.5 and 1 l of hemorrhagic fluid drained, respectively (Fig. 1).



Fig. 1 Multiple lymphatic malformations (x) and a chest wall deformation are clearly seen under computed tomography scan, July 31, 1995.

In November 1995, after a total dose of 220 mg Ukrain had been administered, the patient began to move, and in December 1995, after a total administered dose of 260 mg, he began to speak his first words. By 1996, the patient could stand, and by 1997 the patient could both speak and walk.

However, on the basis of Decree GZ 21.405/1117-II/A/8/93 of February 25, 1994, of the Austrian Ministry of Health, Sport and Consumer Protection, Ukrain therapy was discontinued.

On October 9, 1998, partial resection of a left intrascrotal lymphangioma and a left thoracic lymphangioma with subsequent drainage were performed.

At the beginning of 2000, the patient's condition worsened. Tumor progression caused spinal cord compression, and paraplegia occurred. On January 15 the patient could no longer walk. On March 23, 2000, an extended resection of a thoracolumbal lymphangioma on the back and complex grafting were performed in the Department of Pediatric Surgery at the Donauspital in Vienna. The body weight before surgery was 22 kg and the weight of the ablated tumor was 10 kg. Following surgery the patient remained in a coma for 6 weeks. The patient was on assisted ventilation due to the weakness of the respiratory muscles, and morphine was administered four times a day due to severe pain.

In August 2000, two decubital ulcers developed over the right trochanter and the right shoulder blade. Paraparesis extended to Th5. The decubital ulcers were treated surgically. After discharge from the hospital, a portable ventilator had to be used and morphine administration continued at home. The patient's state seemed hopeless to the hospital physicians (Donauspital, Vienna) and they recommended resumption of treatment with Ukrain.

Therapy with Ukrain 5 mg, i.v., twice a week was resumed on an outpatient basis. Additionally, topical application of Ukrain in gauze compresses was begun. After 3 months of treatment, the patient no longer

complained of pain, and morphine administration was discontinued. After 2 years of therapy, the ventilator was no longer needed. The decubital ulcers healed without skin defects.

## Discussion

Treatment options for lymphangioma include surgery and sclerotherapy. Surgical treatment is challenging. Complete excision is often impossible due to the risk of damage to vital or functionally important surrounding structures. In addition, the cosmetic outcome after such radical surgery may be unacceptable, especially in children. Generally, the results of surgical treatment are currently assessed as unsatisfactory with a high incidence of recurrence and nerve damage. The case presently reported also demonstrates the high risk which accompanies surgical treatment of lymphangioma.

Several other treatment options have been used to treat lymphangioma. These include laser therapy (6); IFN-alpha (7); and various intralesional sclerosing agents, e.g., boiling water, quinine, sodium morrhuate, urethane, iodine tincture, nitromin, steroids, hypertonic saline and ethanol. While little success has been reported using these options, various side effects have been observed (8). In the present case described, 60% dextrose solution was used for intralesional sclerosing therapy with little success. OK-432 (Picibanil) and bleomycin are currently the most frequently used sclerosing agents, giving quite good results (1, 9-13). However, in patients who have undergone prior surgery, the success rate is significantly lower than in primary cases due to the obliteration of communications between cysts following the earlier therapy (9).

This is the first case report of the use of the anticancer drug Ukrain in the treatment of a benign multiple tumor. Ukrain is known for its low toxicity, and its

safety was confirmed in this case. Although the course of the disease was complicated by major psychomotoric and developmental problems, the use of Ukrain was of clear benefit and improved both the general development of the young patient and the course of the disease.

The positive dynamics of the disease following the administration of Ukrain, the recurrence of disease after discontinuation of Ukrain, and the improvement in status after resumption of Ukrain therapy, all indicate that the therapeutic benefit was not a coincidence, but rather the result of the specific activity of Ukrain. The period in which administration had to be discontinued for nonclinical reasons must be regarded as a lost opportunity to heal a growing child.

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