Cavernous lymphangioma of the leg in children treated by the injection of OK-432 after resection

D. Kobayashi, H. Kumagai, S. Satsuma
From Kobe Children’s Hospital, Japan

We describe the treatment of three boys with cavernous lymphangioma of the legs. The suggested guidelines for treatment are extensive surgical resection, although complete resection is usually impossible, and approximately two weeks after the operation aspiration of serous fluid which has accumulated at the operation site, followed by injection of OK-432 (Picibanil). There was pyrexia and local inflammation for several days but the accumulation of serous fluid disappeared after the injection. There were no complications with no recurrence, joint contracture, or pain during a mean follow-up of 48 months (24 to 72).

We conclude that an injection of OK-432 after surgical resection of cavernous lymphangioma of the legs in children is an effective treatment.

Lymphangioma is a congenital malformation of the lymphatic system which usually occurs in children before the age of two years. In approximately 50% of cases, it is present at birth. It may occur in the face, neck, axilla and limbs. Histologically, it is benign and can be subclassified into cavernous lymphangioma and cystic hygroma on the basis of the mean size of the sinuses. Cavernous lymphangioma usually involves the limbs. Surgical resection has been the treatment of choice, but the results have been unsatisfactory.1-3 It invades the surrounding structures so that local recurrence is common and the complication rate is high.

Recently, the intralesional injection of OK-432 (Picibanil, Chugai, Tokyo, Japan), which was developed as an anticancer agent showing immunopotentiation, has been reported to be useful in the treatment of lymphangioma of the face, neck and axillae.4-10 Ogita et al9 demonstrated marked or complete regression in 31 of 46 patients with lymphangioma after intraliesional injection of OK-432. The only adverse reactions were a temporary elevation in temperature and local inflammation. Our aim, therefore, was to assess the efficacy of the injection of OK-432 after resection of cavernous lymphangioma of the legs in children.

Patients and Methods

We treated three boys with cavernous lymphangioma present in the legs at birth. The diagnosis was confirmed by biopsy. The ages of the patients at operation were 11 months, 3 years and 7 years 2 months. The mean follow-up period was 48 months (24 to 72). Treatment involved resection followed by injection of OK-432.

Resection. After assessing the extent of the tumour preoperatively by MRI, we attempted a complete resection. Since differentiation between the tumour and the surrounding normal tissues was very difficult, this proved to be impossible. As a result, the resection, although extensive, was not complete in each child.

Injection of OK-432. Approximately two weeks after surgery, there was accumulation of lymphatic fluid in the operated area. Before its injection, signed consent for the use of OK-432 was obtained. The accumulation of fluid was aspirated completely, and 20 ml of OK-432 (0.01 mg/ml saline) injected at the same site as described by Ogita et al.8,9 Additional injections were not necessary as a satisfactory response was obtained with a single injection in each patient.

Results

A temporary pyrexia (38°C to 39°C) was noted approximately 12 hours after the injection and lasted for between two and four days. There was also localised inflammation in the injected area which lasted for between four and seven days. The local accumulation of fluid did not recur after the injection. There was minor induration for about two months.

One patient developed hypertrophy of the operation scar which required plastic surgery later. There was no recur-
rence of the tumour during a mean follow-up period of 48 months (24 to 72) and no evidence of pain or joint contracture.

**Illustrative case reports**

**Case 1.** An 11-month-old boy presented with a soft-tissue swelling of the left leg which was present at birth and which had continued to enlarge. An excisional biopsy was carried out resecting the affected skin, underlying fascia and fat. Histological examination showed a cavernous lymphangioma. Two weeks after surgery, the fluid (approximately 45 ml) which had accumulated at the site of operation was aspirated completely and OK-432 was injected at the same site. The day after the injection the patient complained of mild pain and his temperature was elevated for three days. There were no other significant complications. He subsequently developed a hypertrophic scar which required plastic surgery (Fig. 1). When examined four years after the operation, he had no pain and was satisfied with the result.

**Case 2.** A three-year-old boy presented with a soft-tissue swelling of his right lower leg which had been present from birth. MRI showed a mixture of high and low signals in both T1- and T2-weighted images. As the tumour had gradually enlarged since birth, surgical treatment was undertaken. The tumour had infiltrated the skin, subcutaneous tissue and underlying fascia. Histological examination of a biopsy specimen revealed various sizes of lymph vessels and confirmed the diagnosis of cavernous lymphangioma (Fig. 2). OK-432 was injected 16 days after operation, following complete aspiration of the fluid at the site of operation. There was mild local inflammation for several days. Two years after the operation he was free from symptoms and there was no recurrence of the tumour.

**Case 3.** A seven-year-old boy presented with two large, soft-tissue masses in the left leg which had been present since birth (Fig. 3a). At the age of three years, a biopsy was performed and the diagnosis of cavernous lymphangioma confirmed. The tumours slowly enlarged (Fig. 3b) and resection was undertaken when he was aged 7 years 2 months. The tumour involved skin, fat, fascia and underlying muscle (Fig. 3c), so that extensive, but not complete resection, was undertaken. Subsequently, an accumulation of serous fluid was aspirated and OK-432 was injected. There was a mild pyrexia for four days after the injection, but there were no other significant complications. Six years after operation, there was no recurrence, no joint contracture, and no hypertrophy of the scar.

**Discussion**

Lymphangioma is a malformation which arises from sequestration of lymphatic tissue which fails to communicate normally with the lymphatic system. The most common clinical finding is a soft fluctuant mass which often enlarges with growth. Although it is considered to be a benign lesion, it may cause symptoms because of its size, the presence of pain, or a tendency to become infected. In the past, surgical treatment has been recommended, but the results have not been generally successful. Harkins and Sabiston² reported recurrence in 12 of 27 patients after resection. Blair et al¹ stated that after attempted excision of cavernous lymphangioma in the arms, recurrence and a high rate of complications can be expected. The reason for this poor prognosis is that the tumour invades surrounding tissue, so that differentiation between tumour and normal tissue is difficult. Complete excision offers the best chance of cure, but is often impossible without sacrificing important neurovascular and other structures. The accumulation
of fluid, which derives from residual lymphatic vessels, also causes poor results.

In 1987, Ogita et al. reported intralesional injection of OK-432 as an alternative treatment for lymphangioma. OK-432 is a sclerosing agent, which is a lyophilised mixture of a low-virulence strain of penicillin G-treated group-A Streptococcus pyogenes of human origin. The mechanism of its action in lymphangioma is thought to be by the induction and activation of white blood cells. The cytokines produced by these cells increase the endothelial permeability and accelerate drainage of lymph. This increased lymph flow leads to a shrinkage of the cystic space. Three studies by Ogita et al. have reported that intralesional injection of OK-432 is an effective treatment for lymphangiomas and should be considered as the primary method of treatment.

In our patients, OK-432 was not used as the primary treatment, but as adjuvant therapy after resection. The main reason for not pursuing the method described by Ogita et al. was because the effectiveness of this treatment depends on the histological appearance. The treatment was efficacious in 92% of cases of cystic lymphangioma, usually involving the neck or face but in only 44% of cases of cavernous lymphangioma, usually involving the arms and legs. These differences were thought to be related to the size and intercommunication of the intralesional cysts, which are known to be smaller in cavernous lesions. Therefore, we thought that primary injection of OK-432 for cavernous lymphangioma might be unreliable. We considered that resection would be necessary if the tumour could not be defined as the cystic type by MRI or ultrasonography. We therefore decided to undertake as complete a resection as possible followed by aspiration of the accumulated lymphatic fluid at approximately two weeks and injection of OK-432 as adjuvant therapy.

Hypertrophy of the scar is common after surgical treatment of lymphangioma. The accumulation of fluid derived from residual lymph vessels, is thought to be one of the causes of this complication. One patient (case 1) developed hypertrophy of the scar postoperatively which required plastic surgery. It is impossible to prove whether or not the temporary inflammatory reaction caused by OK-432 could have caused this hypertrophy, but we think that it is unlikely.

The injection of OK-432 after resection of cavernous lymphangioma in the lower leg in children has been effective in these three patients with no significant complications. We would suggest that a further study of its use in a larger group of patients should be undertaken.

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References


