Ⅳ. 研究成果の刊行物・別冊

No potential conflict of interest relevant to this letter was reported.

1. Bolland MJ, Grey AB, Ames RW, et al. The effects of seasonal variation of 25-hydroxyvitamin D and fat mass on a diagnosis of vitamin D sufficiency. Am J Clin Nutr 2007;86:959-64.
2. de Boer IH, Ioannou GN, Kestenbaum B, Brunzell JD, Weiss NS. 25-Hydroxyvitamin D levels and albuminuria in the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 2007;50:69-77.
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THE AUTHOR REPLIES: García de Tena and colleagues point to cohort studies suggesting an inverse association between serum levels of 25-hydroxyvitamin D and hypertension and the potential positive effects of vitamin D supplementation on blood pressure which may be mediated through the renin–angiotensin–aldosterone system. I would agree there is biologic plausibility to their argument. However, the lack of evidence from randomized, controlled trials and the conflicting data from other prospective cohort studies measuring vitamin D intake and incident disease, rather than serum levels of 25-hydroxyvitamin D, make recommendations regarding vitamin D supplementation in patients with hypertension and below-target values of 25-hydroxyvitamin D somewhat tenuous.[1]

Welsh and colleagues make an important point by suggesting that reverse causality and residual confounding could contribute to the observed associations between levels of serum 25-hydroxyvitamin D and incident disease. I agree completely and would reinforce their cautionary note about the limitations of existing data sets. With respect to the comments by Weiss and Litonjua regarding the putative role of vitamin D as an environmental factor that could influence genomic programming: I agree that this remains a testable hypothesis, and the results of the VDAART may be very valuable in that regard.

De Boer and colleagues raise a valid concern about racial or ethnic and seasonal influences on optimal concentrations of 25-hydroxyvitamin D. Several large studies confirm a seasonal variation of upward of 25% in serum levels of 25-hydroxyvitamin D at certain latitudes, and in the recent Institute of Medicine (IOM) report,[1] this effect was not only recognized but also discussed in regard to supplementation with both calcium and vitamin D.[2,3] Indeed, the IOM committee was so concerned about the data on seasonal variation that they elected to define dietary requirements by examining studies involving persons residing in northern latitudes. Clinically, this could be translated to mean that the optimal time to measure levels of serum 25-hydroxyvitamin D in patients would be during the winter months, when the concentration of vitamin D would be at its nadir. However, it should be noted that the IOM report was focused on a "population" rather than a "medical" model. The authors make an important and clinically relevant point regarding nonwhite populations. Baseline levels of serum 25-hydroxyvitamin D are lower in dark-skinned persons, and their response to supplementation relative to clinical outcomes may differ dramatically from that of whites.[4] The IOM report highlights the need, as stressed by de Boer et al., for much more research involving nonwhite persons who have low serum levels of 25-hydroxyvitamin D.[1]

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Since publication of his article, the author reports no further potential conflict of interest.

1. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: Institute of Medicine, 2011. (http://www.iom.edu/vitaminD.)
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Propranolol for Intractable Diffuse Lymphangiomatosis

TO THE EDITOR: Diffuse lymphangiomatosis is a rare congenital disease with a usually poor prognosis, especially for children with thoracic lesions. Current therapies include surgery, interferon, radiotherapy, and glucocorticoids, but these therapies have side effects, and the treatment strategy

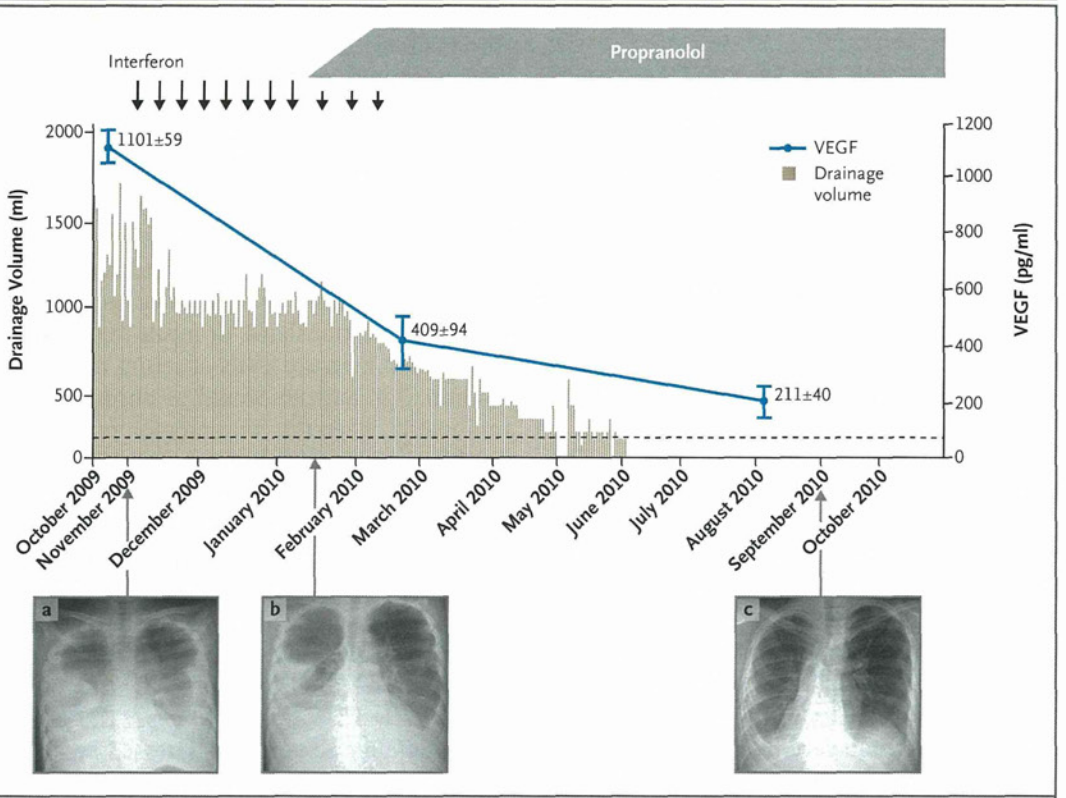

Figure 1. Effect of Therapy with Interferon and Propranolol on Drainage Volume in a 13-Year-Old Boy with Diffuse Lymphangiomatosis with Associated Improvement as Seen on Chest Radiography.

remains controversial.[1] In contrast, for another tumor of vascular origin, infantile hemangioma, propranolol is a new first-line therapy.[2] We report an excellent effect of propranolol in intractable diffuse lymphangiomatosis in a child.

A 13-year-old boy presented in severe respiratory distress on September 5, 2009. Radiography of the chest showed bilateral massive pleural effusions. He had been treated for diffuse lymphangiomatosis associated with chylothorax with regular injections of pegylated interferon alfa-2b.[3] However, because of moderate side effects, including high fever, headache, and depression, the dose of interferon had been reduced and the treatment interval was prolonged in May 2009. Then respiratory distress recurred. Despite restarting pegylated interferon therapy on September 23, 2009, the volume of chylous fluid that was drained remained more than 1000 ml per day from September 2009 through January 2010 (Fig. 1, insets a and b).

Studies have suggested that vascular endothelial growth factor (VEGF) is not only an angiogenic factor but also a lymphangiogenic factor.[4] Propranolol is thought to cause down-regulation of the RAF mitogen-activated protein kinase signaling pathway with reduced expression of VEGF and direct induction of apoptosis in capillary endothelial cells.[5] Since the plasma VEGF level in this patient was very high (normal value, 38.3 pg per milliliter), we hypothesized that propranolol might inhibit lymphangiogenesis and reduce tumor growth.

The protocol of propranolol therapy was approved by the institutional review board at Gifu University, and appropriate written informed consent was obtained. Treatment with propranolol was initiated on January 15, 2010, at a dose of 5 mg every 8 hours (0.5 mg per kilogram of body weight per day) and then gradually increased to 40 mg every 8 hours (4 mg per kilogram per day). The drainage volume decreased gradually, and treatment with pegylated interferon was discontinued. The patient subsequent-

ly returned to school and has received daily oral propranolol for 10 months (Fig. 1, inset c). The blood VEGF level decreased remarkably after the administration of propranolol. However, it is premature to conclude that the reduction in VEGF defines its role in the mechanism of action.

The prognosis for patients with diffuse lymphangiomatosis is poor if the condition is resistant to standard therapies. Propranolol treatment is safe in children and may be an important alternative in the treatment of this disease in infants and children.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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CORRECTIONS

Variability in the Measurement of Hospital-wide Mortality Rates (December 23, 2010;363:2530-9). In the final sentence of the third paragraph (page 2531), "commercial" should have been omitted. In the first paragraph of the Study Design subsection of Methods (page 2531), the second sentence should have read, "Five commercial vendors responded and produced four methods. The joint method submitted by Premier and UHC is experimental and not currently available commercially," rather than "Five commercial vendors responded, and two elected to develop a joint method, resulting in four methods for inclusion in this study." Finally, in the Discussion (page 2534), the second paragraph should have begun, "Three of the four methods for assessing hospital-wide mortality that we studied are currently marketed to hospitals to support internal quality-improvement activities. The fourth method was jointly developed by two commercial vendors who currently market their individual products to hospitals," rather than "The four commercially available methods for assessing hospital-wide mortality that we studied are marketed to hospitals to support internal quality-improvement activities." The article is correct at NEJM.org.

Cerebrospinal Fluid Leak (October 1, 2009;361:e26). In the second paragraph (page e26), the second sentence should have read, "Magnetic resonance imaging revealed a pituitary macroadenoma measuring 17 by 12 mm, with an enlarged adenohypophysis (Panel C, arrow) with a cystic component (Panel C, arrowhead) and a normal neurohypophysis, which . . ," rather than ". . . measuring 17 by 12 mm, with an enlarged adenohypophysis (Panel C, arrow) and a normal neurohypophysis (Panel C, arrowhead), which . . . ." The article is correct at NEJM.org.

Progress and Deficiencies in the Registration of Clinical Trials (February 19, 2009;360:824-30). In the reference list (page 830), the last reference should have been "Lenzer J, Brownlee S. Antidepressants: an untold story? BMJ 2008;336:532-4," rather than "Lenzer J. FDA warns about using antipsychotic drugs for dementia. BMJ 2005;330:992." The article is correct at NEJM.org.

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Propranolol as an Alternative Treatment Option for Pediatric Lymphatic Malformation

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Lymphatic malformation (LM), which was previously termed lymphangioma, is a rare congenital malformation of the lymphatic system and its treatment is still challenging. Propranolol (beta blocker) has been recently developed as a first-line treatment of infantile hemangioma. Our study aimed to assess the effect of propranolol on pediatric LM and the relationship between its effectiveness and vascular endothelial growth factor (VEGF) family members (VEGF-A, C and D). Six Japanese patients with LM (age range: 10 months-19 years old; 2 macrocystic, 2 microcystic and 2 combined type) were enrolled. Oral propranolol was administered at 2 mg/kg/day. The efficacy of propranolol for LM was evaluated by the rate of volume change as calculated from MRI imaging and by symptomatic improvement. In all patients, there were no significant side effects. Patients 3 and 5 were classified as objective responders with tumor volume reduction of 30.6% and 22.9%, respectively, at 24 weeks. Patient 1 showed 8% tumor volume reduction and patient 6 showed symptomatic improvement, hence, both were classified as minimal responders. The other two patients were classified as non-responders. Plasma VEGF-A, C, and D levels were significantly higher in the LM group than in the controls (all $P < 0.01$ by Mann-Whitney test). VEGF-A and D levels at 24 weeks were significantly lower than those at pre-treatment ($P = 0.031$, 0.047 by Wilcoxon matched pairs test). Though further trials with this treatment must be carried out, we propose that propranolol may be an alternative therapy option for intractable LM.

Keywords: beta blocker; lymphangioma; lymphatic malformation; propranolol; vascular endothelial growth factor
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Lymphatic malformation (LM) is a rare congenital malformation of the lymphatic system, which usually occurs in children before the age of two years (Wiegand et al. 2008). LM was previously termed lymphangioma. Surgical excision and sclerotherapy have been used for LM. However, local recurrence is common and the complication rate is high (Marler and Mulliken 2005). Therefore, the treatment of LM remains challenging.

Propranolol is a non-selective beta blocker that is used for the treatment of a variety of cardiovascular diseases. Since the report of Léauté-Labrèze et al. (2008), propranolol has been widely used for the first-line treatment of infantile hemangioma (IH). We reported successful propranolol treatment of intractable diffuse lymphangiomatosis with thoracic involvement (Ozeki et al. 2011). Propranolol is thought to cause down-regulation of the Raf mitogen-activated protein kinase signaling pathway, with reduced expression of vascular endothelial growth factor (VEGF) (Storch and Hoeger 2010). Because plasma VEGF levels in our diffuse lymphangiomatosis patient were high before treatment and were reduced after successful treatment, we hypothesized that propranolol inhibits lymphangiogenesis and reduces LM growth by inhibition of VEGF. Multiple lesions with increased VEGF staining have been reported in LM specimens histologically (Sidle et al. 2005). Therefore, we considered that propranolol could have a beneficial effect on LM as in diffuse lymphangiomatosis.

The VEGF family is involved in the development and growth of the vascular endothelial system. Originally VEGF-A, the founding member of the VEGF family, was simply termed VEGF. VEGF-A is a potent growth factor for blood vessel endothelial cells. VEGF-C and VEGF-D have recently been recognized as playing a role as lymphatic system regulators (Alitalo and Carmeliet 2002).

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We report a clinical trial of propranolol administered to patients with LM and the relationship between plasma levels of VEGF family members (VEGF-A, C and D) and the effectiveness of propranolol treatment.

Methods

Patients

This study protocol was approved by the Ethical Committee of the Graduate School of Medicine, Gifu University. Consent to review patient records and for treatment of propranolol (off-label indication) was received from patients or parents whose children participated in this study in accordance with our institutional ethical standards. Inclusion criteria were as follows: aged from 1 month to 20 years; a stable clinical condition before the study; no history of asthma; reactive airway disease; impaired renal dysfunction; heart defects; arrhythmia; or central nervous system disorders.

Study protocol

The study design is detailed in Fig. 1. Before the start of treatment, the protocol included a clinical examination, echocardiography, electrocardiogram, recording of baseline heart rate, blood pressure, and clinical photographs. Patients were admitted for 5 days of observation at the initiation of treatment. On the first day, oral propranolol was administered at 0.5 mg/kg/day, divided into 3 doses, it was increased to 1 mg/kg/day on the second day, if tolerated well, and further increased to 2 mg/kg/day from day 4, which is well below the dose given for IH. Vital signs and blood sugar levels were monitored 1 hour after administration of each dose of medication, and continuous electrocardiogram monitoring was performed during the patients' sleep. Follow-up visits were performed every 4 weeks, including clinical examination, measurement of vital signs, and clinical photographs. Apart from medication with propranolol, no alternative or adjuvant therapies were performed. The response to propranolol treatment was assessed clinically and radiologically. Digital photographs were taken by the same primary physicians who produced standardized images, using the same views and settings as in the baseline image. Magnetic resonance imaging (MRI) was performed at pre-treatment, and at 12, 24 and 48 weeks after the initiation of treatment. Tumor volumes were calculated by using MRI in both coronal and sagittal views. The primary outcome was the rate of tumor reduction and symptomatic improvement at 24 weeks. Assessments of response were classified as a good response if there was a reduction in size greater than 50%. Patients showing a degree of improvement greater than 10% and less than 50% were rated as an objective response. Patients showing minimal reduction less than 10% or transient improvement of symptoms were classified as having a minimal response. Finally, patients showing no improvement were classified as no response.

Laboratory tests for plasma VEGF levels during treatment

Peripheral blood samples were obtained at the time of pretreatment, and at 4, 8, 12, and 24 weeks after the initiation of treatment. All blood samples were centrifuged at 1,000 × *g* for 30 minutes. Plasma was separated, aliquoted, and stored at −80°C until analysis was performed. Plasma VEGF levels were determined using a commercially available monoclonal antibody-based enzyme-linked immunoassay kit designed to measure each type of VEGF according to the manufacturer's instructions (Quantikine; R&D Systems, Minneapolis, MN, USA). The sensitivities of VEGF-A, C, and D were 5.0 pg/ml, 4.0 pg/ml, and 4.7 pg/ml, respectively. Optical density was measured at 450 nm using an automated microplate reader. We also measured VEGF levels from samples from 30 control children ranging from 2 months to 17 years old (mean ± SE: 3.9 ± 0.7 years old) for references.

Statistical analyses

Significance of differences in the VEGF levels between the LM group and control group before treatment was tested using the Mann-Whitney test. Significance of differences in VEGF levels between pre-treatment and 24 weeks after treatment was tested using the Wilcoxon matched pairs test. A P value of less than 0.05 was considered statistically significant. All analyses were performed using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA).

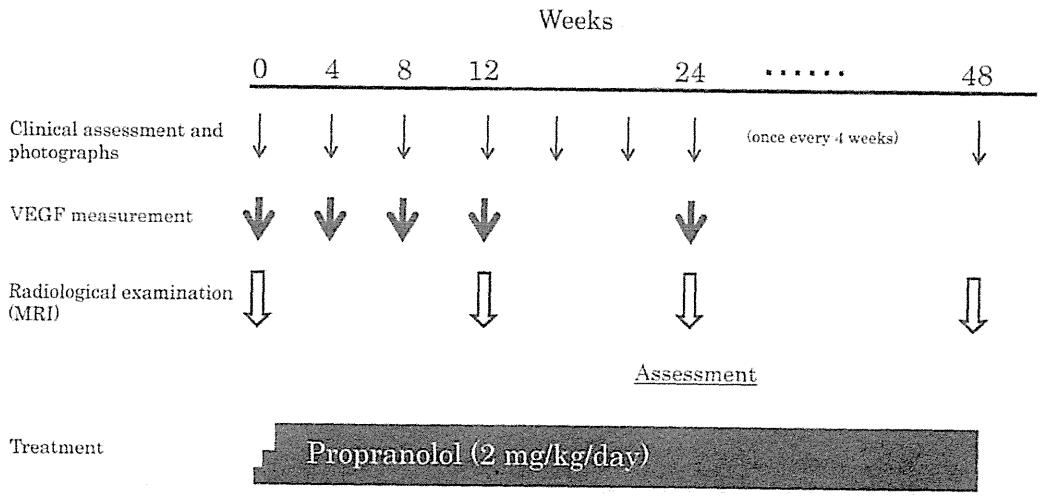

Fig. 1. Study protocol.
The LM patients underwent propranolol therapy, and its safety and efficacy were determined during a routine schedule.

Results

Patient characteristics are shown in Table 1. All patients were evaluated and treated at our institution between 2010 and 2012. A total of 6 patients (2 boys and 4 girls; age range: 10 months-19 years old; mean ± SE: 6.7 ± 3.6 years old) were enrolled. LM was identified at birth in all patients. We classified LM into 3 subtypes as follows: cysts larger than 2 cm in diameter were classified as "macrocystic"; those smaller than 2 cm in diameter were "microcystic"; and mixed lesions were "combined". Treatment modalities used before propranolol therapy consisted of sclerotherapy (OK-432 injection) and an operation. All patients included in the study were able to complete the treatment program, and there were no dropouts.

In six patients, there were no good responders. Two patients (patients 3 and 5) showed an objective response and LM was decreased in the initial stage of treatment. The clinical course of objective responders was as follows.

Patient 3, a 10-month-old boy, presented with a large, soft-tissue mass in the left lower leg since birth. At the time of admission, there was limited motion of the left ankle joint because of subcutaneous edema (Fig. 2A). Gadolinium-enhanced MRI showed a mixture of enhanced and non-enhanced lesions in the subcutaneous tissue of the lower thigh and toe (Fig. 2B). Surgical resection or sclerotherapy was considered to be difficult because of the risk of recurrence and complications. The patient was enrolled in our study with the consent of his parents. Several days after initiation of treatment, the skin turgor gradually decreased and skin creases appeared. After 4 weeks, the leg swelling was diminished and the joint stiffness had improved. The percentage of the calculated volume of the total lower left leg was reduced (Fig. 2C). The gadolinium-enhanced lesion was predominantly diminished. The volume of the dorsum of the foot, which was not enhanced by gadolinium, increased in parallel with the growth of bone and muscle.

Patient 5, a 1-year-old boy, presented with a combined (macrocystic and microcystic) LM of the left neck (unilateral, infrahyoid, and suprahyoid) since birth. At 20 days of age, partial resection was performed to reduce dyspnea, and the histological diagnosis of LM was made. The tumor grew continuously and he received a local injection of OK-432 for the macrocystic LM at 1 month of age. However, the sclerotherapy resulted in airway obstruction and airway intubation was necessary for 1 month. At 1 year of age, because surgical resection of the whole lesion appeared to be difficult, he was referred to our hospital to receive propranolol treatment (Fig. 2D). Several days after initiation of treatment, the pericystic skin gradually softened. Similar to patient 3, the MR gadolinium-enhanced lesion showed a reduction in volume, and the paratracheal lesion disappeared (Fig. 2E). The percentages of calculated volumes of the total LM and gadolinium-enhanced lesion were reduced at 24 weeks (Fig. 2F).

Two patients (patients 1 and 6) showed minimal reduction of less than 10% or transient improvement of symptoms. Patient 1, a 19-year-old woman with macrocystic LM of the left neck and mediastinum, showed a minimal reduction of 8% at 4 weeks. Patient 6, a 17-year-old woman, with combined LM of the right neck and maxillo-

Table 1. Characteristics of LM patients treated with propranolol.

Patient number	Sex	Type	Localization	Age at initiation of propranolol treatment	Indication for treatment	Previous treatments	Adverse effects	Duration of propranolol treatment (mo)	Response
1	F	Mac	Rt neck, mediastinum	19 y	CR, FR (pain)	-	Lightheadedness	8	MR (tumor reduction)
2	F	Mac	Lt back	1 y	CR, FR (pain)	-	-	6	NR
3	M	Mic	Lt lower thigh	10 mo	CR, FR (limited ankle extension)	-	-	18	OR (tumor reduction, improvement of joint stiffness)
4	F	Mic	Rt facial	1 y	CR, FR (fused eyelids, amblyopia)	-	-	15	NR
5	M	Combined (mac, mic)	Lt neck	1 y	CR, FR (dyspnea)	Partial resection, sclerotherapy	-	13	OR (tumor reduction)
6	F	Combined (mac, mic)	Rt neck, maxillofacial area	17 y	CR, FR (bleeding, pain, stomatitis)	Operation	Lightheadedness	6	MR (improvement of bleeding)

M, male; F, female; Mac, macrocystic; Mic, microcystic; Rt, right; Lt, left; y, year; mo, month; CR, cosmetic risk; FR, functional risk; MR, minimal response; OR, objective response; NR, no response

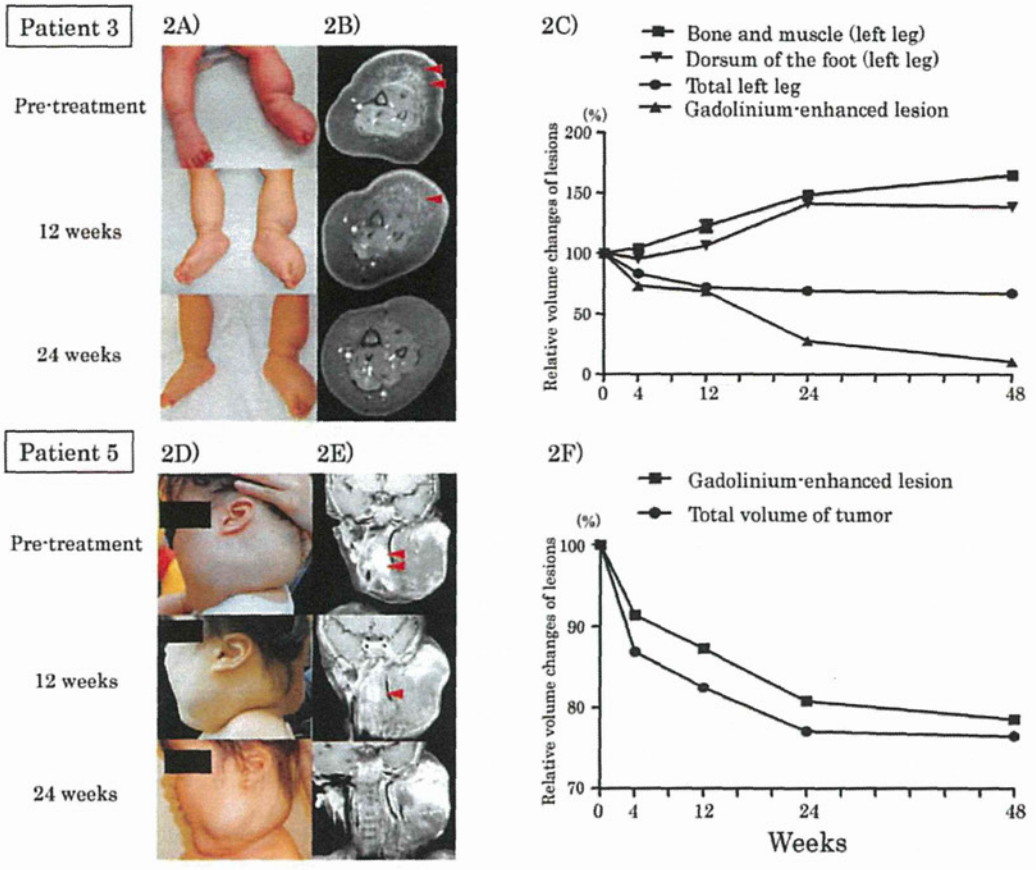

Fig. 2. Photographic documentation, gadolinium-enhanced MRI, and relative volume changes of lesions in patients 3 and 5. (A, B) Clinical photograph and enhanced MRI pre-treatment, and at 4, 8, 12, and 24 weeks in patient 3. The red arrowheads indicate the MR gadolinium-enhanced lesion. (C) Relative volume changes of the LM through 48 weeks of treatment in patient 3. Data are expressed as the means of three independent calculations. Volume changes in both bone and muscle indicate growth of the patient's leg since 10 months of age when the treatment was started. (D, E) Clinical photographs and enhanced MRI at pre-treatment and at 4, 8, 12, and 24 weeks. (F) Relative volume changes of the LM through 48 weeks of treatment in patient 5.

facial area, had pain and bleeding from microcystic lesions of the oral mucosa. Several days after treatment, the bleeding stopped and the pain disappeared. No change was observed in the size of LM. Two patients (patients 2 and 4) showed no response.

In all patients, there was no significant side effect during treatment. The two teenagers (patients 1 and 6) had transient lightheadedness and a mild headache. We evaluated hemodynamic variables during admission and on follow-up visits. Transient bradycardia was observed in 1 patient. This episode occurred at night during sleep and was self-limiting. Overall, the adverse events were all mild and transient, and there was no drop-out of patients because of adverse events.

VEGFs at pretreatment and during treatment

Prior to therapy, plasma VEGF-A, C and D levels were significantly higher in the LM group than those in the control group (all $P < 0.01$). VEGF-A and D levels at 24 weeks after treatment were significantly lower than those at pre-treatment ($P = 0.031$, 0.047, respectively). Although VEGF-C levels did not significantly change between pre-treatment and 24 weeks after treatment, VEGF-C levels in objective responders (patients 3 and 5) appeared to be decreased after treatment compared with those in minimal and non-responders (patients 1, 2, 4 and 6). We could not evaluate the statistical analysis because the number of patients was small.

Discussion

We conducted a clinical trial of propranolol therapy for pediatric LM. Among 6 patients, patients 3 and 5 were objective responders who showed obvious symptomatic improvement and had a greater than 10% and less than 50% shrinkage in their tumor volume. The gadolinium-enhanced lesion as shown by MRI was predominantly diminished in these patients. Two patients had some palliation of symptoms, although tumor volume reduction was less than 10%. Hemorrhage from oral mucosal LM was quickly stopped in patient 6. LM patients had higher plasma VEGF levels than those in pediatric controls, and they were decreased by propranolol treatment. These patterns were more evident in

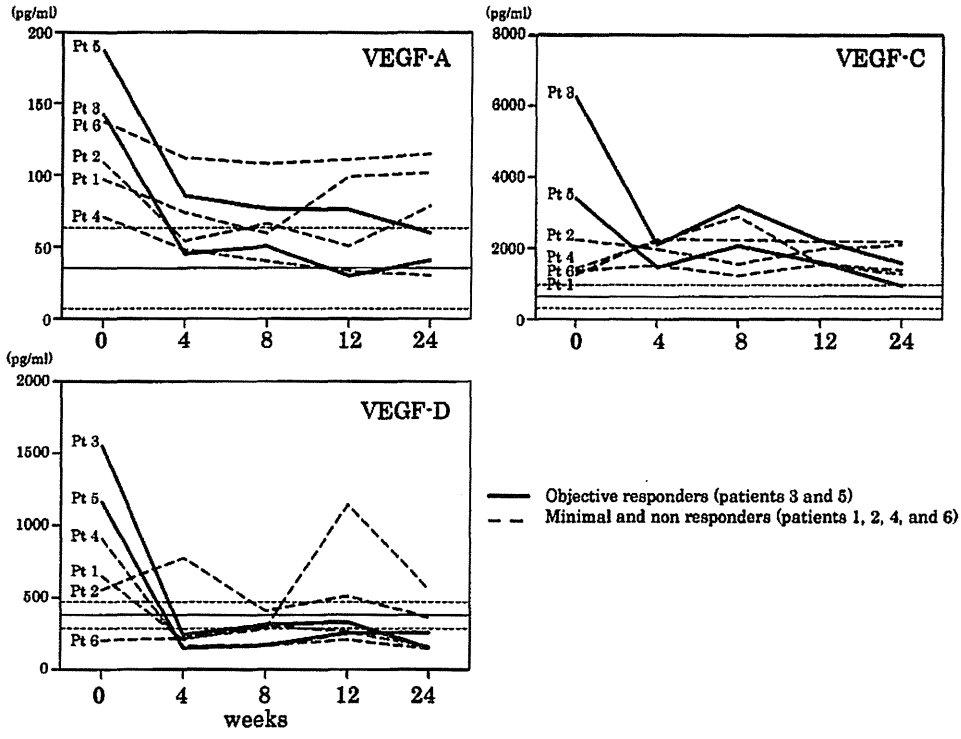

Fig. 3. Plasma VEGF levels in LM patients during treatment.
Each graph shows the plasma levels of VEGF family members (VEGF-A, C and D) during treatment. The horizontal axis represents the time after treatment (weeks). The red solid horizontal lines indicate the mean level of VEGFs in pediatric healthy controls. The red dotted horizontal lines indicate the mean ± standard deviation of VEGFs. Pt: patient.

objective responders. Propranolol might be more effective in patients with gadolinium-enhanced lesions as shown by MRI and high plasma VEGF levels, as discussed below.

Currently, propranolol is widely used and is recommended as the first-line treatment for IH in some sites, especially the airway (Peridis et al. 2011). Treatment of intractable LM is still challenging, especially in patients of cervical LM, such as in patient 5, who was treated by partial resection and sclerotherapy, but whose mixed-type LM had not regressed after 1 year (Fig. 2D). Moreover, he had to be intubated because of airway obstruction caused by inflammation after sclerotherapy. However, propranolol treatment had a favorable effect without an adverse reaction (Fig. 2D). Patient 3 had microcytic LM in his lower leg and had functional problems for walking. This type of LM invades the surrounding structures, so the outcome of surgical resection is generally unsatisfactory. Propranolol showed an objective response and functional improvement (Fig. 2A). Propranolol therapy was apparently effective in intractable LM in the patients who had a reduction in tumor volume.

Patient 6 had clinical improvement for oral bleeding from LM lesion after initiation of propranolol, although no obvious reduction in LM volume was observed. Similar observations have been reported in patients with lingual LM lesions (Leboulanger et al. 2011). Beta blockers inhibit the vasodilation mediated by adrenaline via beta-adrenergic receptors, and this leads to vasoconstriction. Vasoconstriction is reported as an early effect of propranolol on IH (Storch and Hoeger 2010). Propranolol treatment may affect hemorrhagic lesions and improve the quality of life in those who have mucosal bleeding from LM lesions.

The effect of propranolol on reduction of tumor volume varied among patients, and even within LM lesions in patients. We performed an objective assessment using MRI-based volumetric measurements of LM. The results of our study demonstrated that gadolinium-enhanced lesions decreased after treatment in patients 3 and 5. LM in the other 4 patients had no apparent gadolinium-enhanced lesions, and had only a minimum reduction in volume. In LM, gadolinium-enhanced lesions consist of hypervascular or mixed vascular lesions. Therefore, propranolol may have a positive effect on these lesions through blood flow because propranolol treatment reduces lesion volume and vessel density in patients of IH (Bingham et al. 2012). Propranolol might be more effective for LMs with gadolinium-enhanced lesions than for those without such lesions.

Propranolol leads to a reduced expression in VEGF and, therefore, causes an inhibition of angiogenesis (Storch and Hoeger 2010). This effect is one of the important mechanisms of regression of IH. Serum levels of VEGF are elevated in infants during the proliferative phase of IH.

Conversely, the expression of VEGF is significantly reduced during the involution phase, as well as in completely regressed LMs. Propranolol treatment in a patient with intractable diffuse lymphangiomatosis resulted in a reduction in plasma VEGF levels in parallel with clinical improvement. Reduced expression of VEGFs by propranolol causes down-regulation of the extracellular signal-related kinase / mitogen-activated protein kinase cascade, which is important for angiogenesis. Recent studies suggest that VEGFs can act as lymphangiogenic factors (Ferrara 2004). VEGF-C is strongly expressed in patients of microcystic LM compared with patients with other types of LM, suggesting that these patients possess proliferative activity (Itakura et al. 2009). In our study, plasma VEGF levels in LM patients were significantly higher than those in pediatric controls. After treatment, plasma VEGF levels were significantly decreased, especially in objective responders. Plasma VEGF may be a reliable marker of activity of LM and a good indicator of response to therapy.

Our study limitations included a heterogeneous patient population and a small number of patients. Larger trials may confirm these results and provide more detailed information. Medical treatments, including interferon and systemic corticosteroids, have been attempted for patients with extensive inoperable LM, with varying degrees of success. Although these drugs generally have serious side effects, propranolol has been used to safely treat cardiac conditions in children for over 40 years and it is well tolerated with few adverse effects. In conclusion, we propose that propranolol is an alternative treatment for challenging LMs.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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accurate information on prognosis is often difficult to obtain in this condition.

Conclusions

In general, CBT are associated with poor prognosis and only limited information is available at present due to a lack of sufficient cases. Diagnosis during fetal life is difficult. It is important to extensively evaluate the tumor on imaging (location, size and features) and clinical features (gestational age at diagnosis, complications) and select the most appropriate management of pregnancy and the perinatal treatment based on consultation with various specialists. Accumulation of further data is important to clarify the entire clinical picture and establish a management system for this condition.

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Vincristine, actinomycin D, cyclophosphamide chemotherapy resolves Kasabach–Merritt syndrome resistant to conventional therapies

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Key words infant, kaposiform hemangioendothelioma, Kasabach–Merritt syndrome, vincristine, actinomycin D and cyclophosphamide therapy.

When kaposiform hemangioendothelioma (KHE) is accompanied by Kasabach–Merritt syndrome (KMS), it may result in considerable morbidity and mortality.[1,2] The usual treatment for KHE associated with KMS of the extremities includes the use of steroids, coil embolization, radiation therapy and interferon-α. Recently, vincristine (VCR) has also been reported to be effective to control the coagulopathy in KMS.[2–5] In the present case, KMS was resistant to conventional therapies, and so we elected to use VCR monotherapy. Several courses of VCR monotherapy were insufficiently and transiently effective, and the consumptive coagulopathy recurred. Therefore, we decided to treat this patient using combined vincristine, actinomycin D and cyclophosphamide (VAC) therapy. After four cycles of VAC, KMS caused by the left arm hemangioma finally resolved and there has been no recurrence for 6 years. In this case, VAC therapy was effective after failure of repeated VCR monotherapy.

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Case report

A male infant, born at full term by spontaneous vaginal delivery, was noted to have a large hemangioma of the left arm. He presented with anemia and thrombocytopenia at 1 month of age, and was diagnosed with KMS. The patient was referred to National Center for Child Health and Development for treatment of KMS at 2 months of age. First-line systemic therapy with corticosteroids was initiated (prednisolone 2 mg/kg per day) with simultaneous irradiation (10 Gy in five fractions), but it did not affect the tumor size or platelet counts. Subcutaneous injections of $1–3 \times 10^6$ (U/m^2 body surface area) of interferon-α for 1 month and mega-dose methylprednisolone therapy were then attempted, which also failed to improve KMS. At this stage the patient required 2 mg/kg per day of corticosteroids, and also needed frequent platelet transfusions to control bleeding. Transcatheter

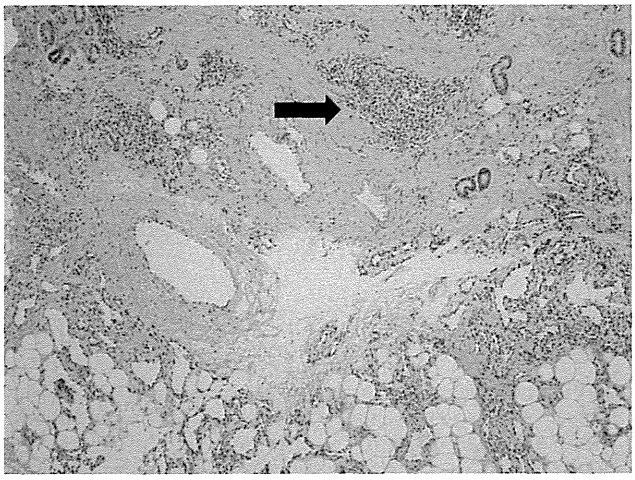

Fig. 1 Histopathology showing kaposiform hemangioendothelioma. The capillary vessels are diffusely proliferating in the fat tissues, and there is evidence of dense hyperplasia of the spindle shape cells (arrow).

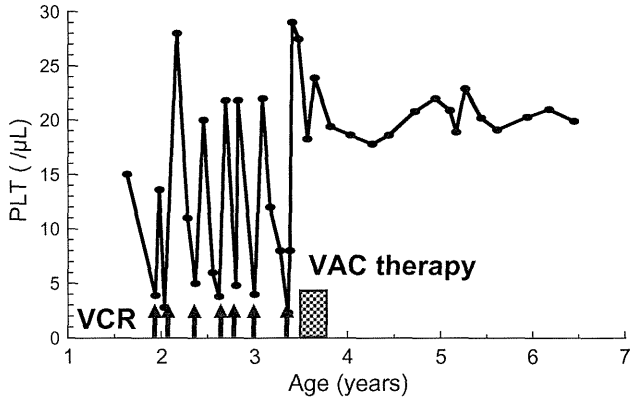

Fig. 3 Platelet counts after vincristine (VCR) or vincristine, actinomycin D and cyclophosphamide (VAC) therapy. VCR was dramatically effective for Kasabach–Merritt syndrome (KMS) but the effect was transient; the tumor showed regrowth and platelet counts repeatedly decreased. After eight courses of VCR monotherapy, the patient was treated with five courses of VAC. Remission of KMS was achieved for >4 years.

embolization of the feeding artery under general anesthesia was attempted three times. This resulted in a transient increase in the platelet counts. KMS relapsed within 2 weeks after the embolization. A biopsy showed that capillary vessels were diffusely proliferating in the fat tissues, and there was evidence of dense hyperplasia of spindle-shaped cells consistent with KHE, which frequently causes KMS (Fig. 1).[1,6–8]

Considering that the therapeutic effects of steroids, interferon-α, radiation, and embolization therapy were limited in the present case, we decided to start VCR. VCR was given weekly at a dose of 1.5 mg/m^2 (body surface area). After 8 weeks of VCR injections, the rate of platelet consumption gradually decreased, and platelet transfusions were no longer required (Fig. 2). After 11 cycles of VCR therapy, platelet counts increased up to 200 000/μL and were maintained at that level for a few months without any treatments. The tumor showed regrowth, however, and platelet counts decreased again 4 months after cessation of VCR therapy (Fig. 3). VCR monotherapy was again applied for recurrent KMS. In this situation, the platelet counts transiently increased after several episodes of VCR, but they gradually decreased after cessation of VCR therapy. After repeating seven doses of VCR monotherapy, at the age of 3 years it was decided to convert to a combination therapy of vincristine, actinomycin D, and cyclophosphamide (VAC). The VAC regimen included vincristine at 1.5 mg/m^2 on day 1, actinomycin D at 0.015 mg/kg on days 1–5 and cyclophosphamide at 10 mg/kg on days 1–3. During VAC therapy there were no serious side-effects. After four cycles of VAC therapy, KMS caused by the left arm hemangioma was finally resolved and there has been no recurrence for 6 years (Figs 3,4).

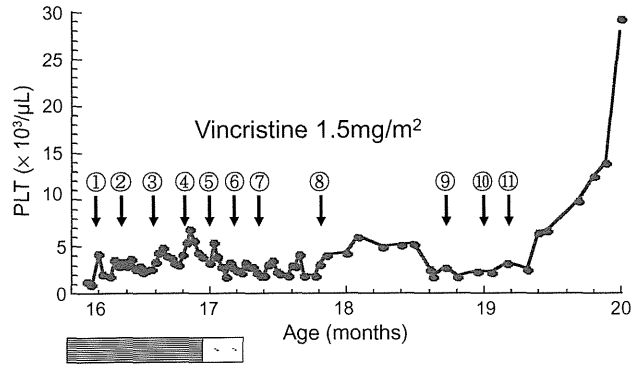

Fig. 2 Platelet (PLT) counts after vincristine (VCR) therapy. PLT infusions were required every day until the fifth VCR injection. After eight courses of VCR the patient did not require PLT infusions, and the PLT count increased from 40 000 to 250 000/μL.

Discussion

When KHE is accompanied by KMS, it may result in considerable morbidity and mortality. In the present case KMS was treated with steroids, coil embolization, radiation therapy and interferon-α, but these therapies were totally ineffective. Biopsy indicated KHE, which often causes life-threatening KMS.[9] Several reports have recently shown VCR to be effective for controlling the decreased platelet counts and potential mortality associated with KMS.[3–6,9–11] In addition, Haisley-Royster *et al.* reported that all four patients in whom KMS relapsed after a first course of VCR therapy, were successfully treated with second courses of VCR.[9] In contrast, the present patient had a relapse of KMS after several doses of VCR monotherapy.

Hu *et al.* reported that combined VAC therapy was effective for intractable KHE associated with KMS, which was resistant to corticosteroid therapy.[7] Because of toxicity considerations, such as veno-occlusive disease, hemorrhagic cystitis, pancytopenia

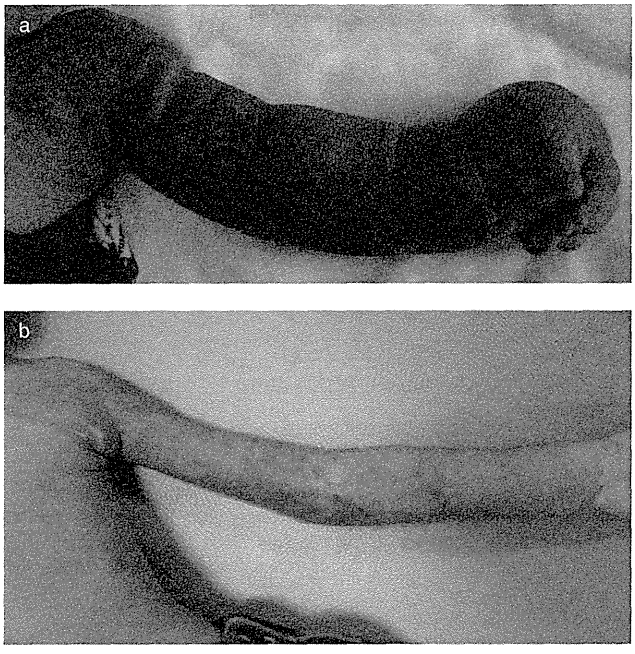

Fig. 4 (a) After six courses of vincristine there was a large, dark-red lesion covering the left arm and upper thorax. (b) After vincristine, actinomycin D and cyclophosphamide therapy, the dark-red lesion of the left arm had largely resolved.

and secondary malignancy, we were initially hesitant to use actinomycin D or cyclophosphamide. Only one case of KHE associated with KMS treated with VAC combination therapy after VCR monotherapy has been reported, but combination VAC chemotherapy was not effective in that report.[12] In addition, no comparative study of VAC combination therapy and VCR monotherapy for KHE associated with KMS has been reported. We decided to treat the present patient with VAC combination therapy because of the persistence of refractory coagulopathy and life-threatening condition.

Gottschling *et al.* reported that cyclophosphamide monotherapy was a safe and effective treatment for patients suffering from life-threatening diffuse hemangiomatosis unresponsive to corticosteroid therapy.[13] Cyclophosphamide monotherapy might have been effective in the present case but the previously reported cases all involved multiple cutaneous and liver hemangiomas, with complications that included high-output failure, and hepatic failure, and did not include KMS.

The present patient was treated with radiation therapy after steroid and interferon therapy. Due to problems with radiation therapy in infants, however, such as cancer or growth disorder, it might be better to treat pediatric patients with VCR or VAC chemotherapy prior to radiation therapy.

Vincristine, actinomycin D and cyclophosphamide therapy resulted in a significant decrease of tumor size, correction of the thrombocytopenia and a complete remission for 6 years in the present patient. The combined therapies of steroids, interferon-α, radiation and embolization were not effective for KHE in this patient. Thus, VAC therapy may provide an alternative therapeutic approach to intractable KMS resistant to conventional combination therapies, even when VCR monotherapy is not effective.

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特集　乳幼児健診でみつかる外科系疾患

Ⅰ．乳幼児健診において外から見てわかる疾患

リンパ管腫

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要旨

リンパ管腫は，頸部，腋窩に多くみられる軟らかい腫瘤として発見される．比較的まれで，出生時外観から明らかになることが多いが，目立たない病変の場合は，親が体の左右差から気づいたり健診で指摘されることもある．診断は超音波検査で容易につけられ，出血や感染があると，急に腫脹し痛みを生じる．リンパ管腫は大きく分けて嚢胞状と海綿状の二つのタイプがあり，外科的切除や硬化療法で改善することが多いが，とくに嚢胞状に対しては硬化療法が有効である．治療に緊急を要することは少ないが，頸部病変の場合に気道狭窄の可能性を念頭におく必要がある．

Key words　リンパ管腫，硬化療法，OK-432（ピシバニール®），lymphangioma，lymphatic malformation

はじめに

リンパ管腫（lymphangioma，近年lymphatic malformationともよばれる）は，おもに小児に見られる良性腫瘤性病変であり，小児外科医は比較的よく遭遇するが，一般的にはあまり知られていない疾患である．病変は特徴的であり，鑑別にあがれば診断は比較的容易である．

リンパ管腫は組織学的にリンパ管内皮に覆われた大小の嚢胞（顕微鏡レベルから数cm大まで）と周囲の間質性組織により構成されている．嚢胞の大きさや間質組織との割合により，大きく嚢胞状（cystic，**図1-A**）と海綿状（cavernous，**図1-B**）に分けられるが，臨床経過・治療の選択もおおまかにこれに左右される（「**治療**」の項，参照）[1]．混合病変も多い．発生部位により，正常軟部組織（筋・腺）内に網の目状に広がり，神経・血管を巻き込んでいるため（**図2**），治療に難渋することがあるが，大部分の症例では満足な治療結果が得られる[2]．

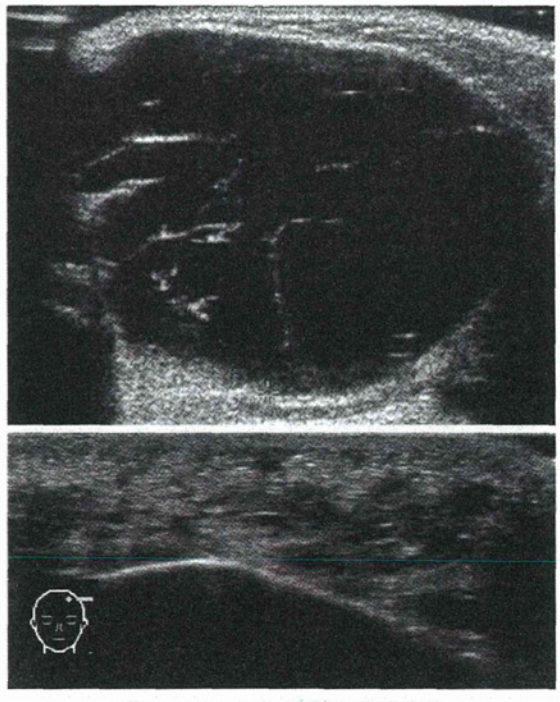

図1　リンパ管腫超音波検査所見
A：頸部嚢胞状リンパ管腫の超音波検査像．低エコーな多数の嚢胞同士の間には薄い隔壁が認められる．病変の大部分を嚢胞が占める
B：前額部海綿状リンパ管腫の超音波検査像．壁のはっきりしない小さな嚢胞が多数低エコーに描出されている．嚢胞間は間質組織が隔てる．病変の大部分は間質組織が占める

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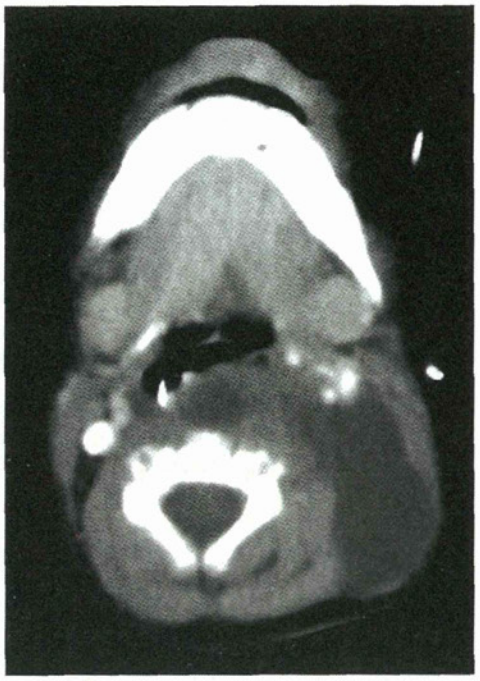

図2　頸部リンパ管腫（造影CT）
左頸部リンパ管腫の2カ月男児．病変は低吸収の嚢胞部分を主体としており，頸部の血管群を巻き込み，咽頭後壁から気道を前方へ圧排している

病　因

病因は明らかにされていない．リンパ管腫は，頸部・腋窩など胎生期にリンパ嚢を形成する部位からの発生が多いことや胎生期から病変が認められるという臨床的特徴より，胎生のリンパ管形成時期になんらかの異常を生じ嚢胞性病変を形成するといわれている[3]が定かではない．発生に関して性差や遺伝性は認められていない[4]．

臨床経過

リンパ管腫は悪性ではないため，それ自体が生命を奪うことはない．病変の部位や大きさによるが，70～80%の症例で治療により病変が消失するか著明に縮小し満足のいく結果が得られる[2)5)]．とくに嚢胞状リンパ管腫の場合によい結果が得られることが多い[1)6)]．また治療せずにいても自然に縮小したり，感染や出血のあと縮小していくこともある[4)6)]．一方，海綿状リンパ管腫は，治療への反応が悪く，病変の縮小はなかなか得られない[1)]．

とくに新生児・乳児期の頸部や縦隔に広がる巨大病変の場合には気道閉塞をきたしやすく（図2），新生児科，小児外科，耳鼻咽喉科，形成外科，麻酔科などでチームを組んで治療にあたらねばならないような重症例もある．通常，診療の中心は小児外科が担当することが多いので早期にコンサルトするとよい．

発生部位

全身ありとあらゆる部位から発生の報告があり（表在，深部臓器を問わず），解剖学上リンパ管のあるところすべてにリンパ管腫は発生しうると考えられる（図3）．とくに多いのが頸部（下顎部から鎖骨上窩），腋窩，縦隔など[2)4)]で，それらにまたがる病変もある．大きさはさまざまで，直径2～3 cmから20 cmを超えるものまである．

症状，外観・触診上の特徴

基本的には突出する無痛性腫瘤[2)]である（図3）が，急性腫脹で発症した場合などは，内出血や感染によることが多く，自発痛・圧痛を生じることが多いが徐々に改善する．

外観上は突出する滑らかな隆起性病変であり，左右を比較して初めてそれとわかるようなわずかな隆起の場合もある．深部（縦隔など）に大部分があり，体表にわずかに突出しているだけの場合もある．

触診では，弾性軟で波動を触知し，中心部の圧迫により腫瘤の辺縁・境界が明瞭になることが多い．ただし，リンパ管腫嚢胞内に出血して急に腫れた場合には，腫瘤は緊満し固く触知する．また病変部に感染が生じた場合には，硬く腫れ，圧痛，皮膚発赤を伴うこともあり，全身症状として発熱も認められる．

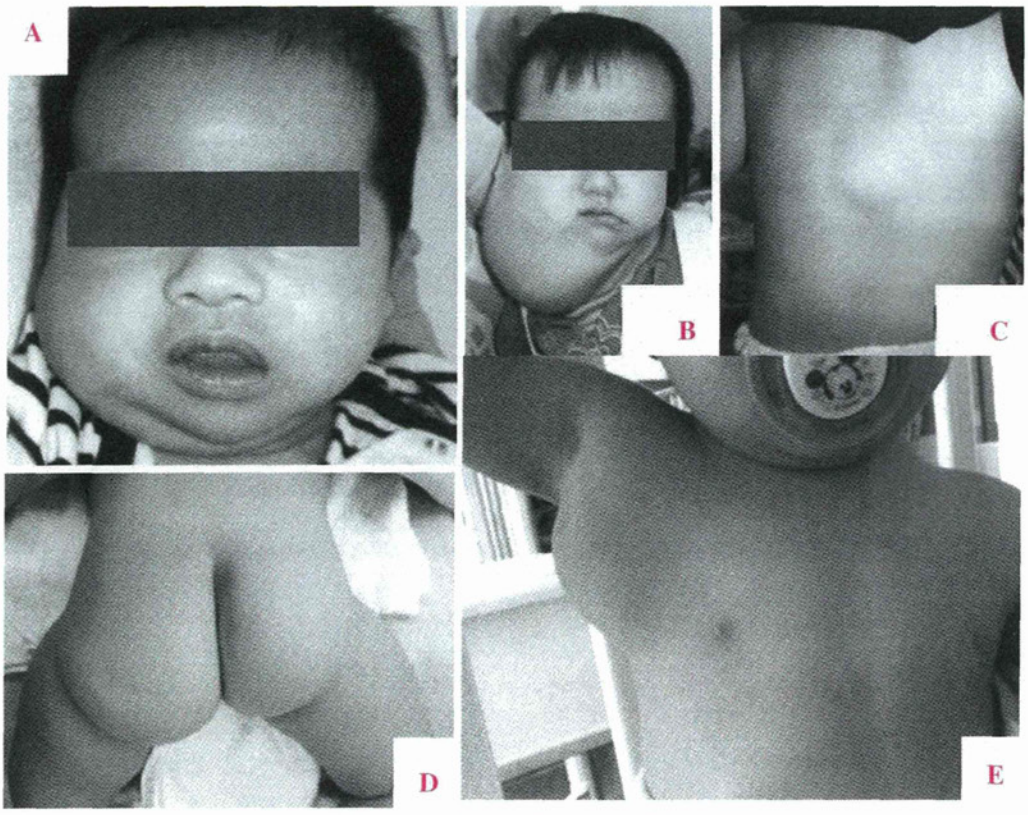

図3　さまざまな部位のリンパ管腫
A：右頸部リンパ管腫（3カ月），B：右頸部リンパ管腫（1歳，治療中），C：背部正中リンパ管腫，D：左殿部リンパ管腫，E：右腋窩リンパ管腫

発症時期

リンパ管腫は多くが先天性に発生すると考えられており，その多く（80%）が乳児期までに発見される[2)4)]．

病変の大きさや部位によっては胎児超音波検査にて検出され出生前診断されることがある[2)]．また，病変が体表にある場合には出生時に外観上明らかであることが多い．目立たない病変の場合，新生児期や乳児期に親が体の左右差から腫瘤の存在に気づいて受診したり，健診で初めて診察医に指摘されたりすることが多い．

幼児期以降は突然腫脹が出現して，本人や家族が気づいて受診に至ることが多い．突然腫れてくる原因はリンパ嚢胞内への出血や感染がほとんどである．

またリンパ管腫は体調により病変部の張りに変化を認めることが多く，体調不良（感冒など）を契機に患部の張りや突出に気づかれることもある．

検　査

問診から視診・触診にてリンパ管腫が鑑別疾患にあがった場合には，まず簡便で正確性が期待できる超音波検査を行う．典型的な嚢胞性病変が描出される（図1-A，B）．嚢胞を含む疾患は多数あり鑑別が必要となることもあるが，その場合にはMRI，CT（とくに造影CT）（図2）が有用である[7)]．

嚢胞内容液を穿刺吸引し，細胞，生化学検査よりリンパ液であれば一応診断できるが必須ではない．確定診断には組織の病理学的検査が必要だが，切除前に生検を行うことはまれである．

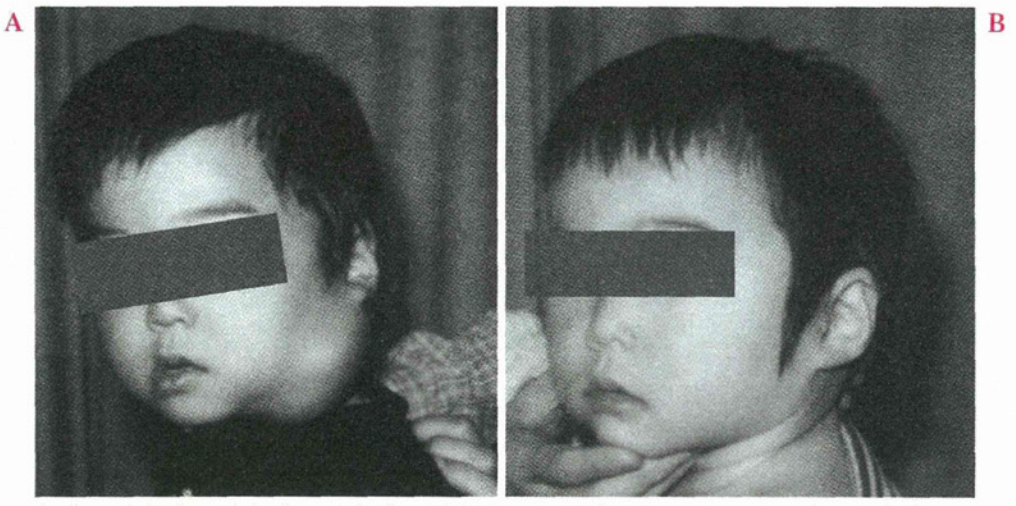

図4　治療前，治療後の外観
左頸部リンパ管腫の男児．治療前（A）とOK-432硬化療法2回施行6カ月後（B）

治　療

リンパ管腫に対する治療は，外科的切除，硬化療法，全身療法に大きく分けられる．

1．外科的切除

リンパ管腫は手術でリンパ液を含んだ大小の嚢胞をすべて取り除くことができれば完治するので，短期間で治療を完了できる[8]．体幹や四肢などの体表にあり切除が容易な場合にはよい適応である．また海綿状リンパ管腫に対しては硬化療法が効かないことが多く，切除術が有効である．気道閉塞をきたすような場合にも早期の解除のため切除を選択せざるを得ないこともある．

手術で切除する際の問題としては，血管・神経・筋肉が病変部に完全に巻き込まれているときなどは，完全切除のためにはこれらの正常な部分も同時に切除せざるを得ず，機能的・整容的な問題を残すことである．したがって，そういった問題を避けるべく病変を部分的に切除することも選択される．またリンパ管腫の特徴として病変部にリンパ液が流入するため，切除した断端からのリンパ液流出が長く続くことがある．創部や漏出するリンパ液を伝って細菌が流入し，感染を生じることもある．

2．硬化療法

リンパ管腫治療において外科的切除と並ぶ治療の柱である．日本では，まず硬化療法の可能性を最初に考慮することが一般的である．薬剤を病変部に注入すると，その反応でリンパ嚢胞が縮小していく．理想的には嚢胞内リンパ液を吸引し，嚢胞内に薬剤を注入するともっとも効果が出ると考えられている．

硬化剤としてはOK-432（ピシバニール®）[5]，ブレオマイシン[9]，無水エタノール，フィブリンなど，さまざまな薬剤が用いられてきた．

日本では現在OK-432が第1選択である．発熱，局所の強い炎症反応（発赤，腫脹，疼痛）が生じるが，後遺症を残すことなく多くの場合には最終的に病変部が縮小する（**図4**）．嚢胞性リンパ管腫にはとくに効果的であることが知られている[5][10]．

ブレオマイシンは世界中で用いられている．リンパ管腫縮小に有効であることが認められているが，用量依存性に肺線維症をおこす可能性があり，第1選択として用いている施設はわが国では少なくなってきている[9]．

上記のように硬化剤は多様だが，どの薬剤も嚢胞状のリンパ管腫には有効で，一方，海綿状リンパ管腫に確実な効果が得られる薬剤は知られてい

ない．

3．全身療法

難治性のリンパ管腫に対しては全身療法も試みられている．インターフェロンやステロイド投与が有効であった症例の報告[11][12]があるが，無効例の報告もある．ごく最近，プロプラノロール（β遮断薬）がリンパ管腫症（後述）に有効であったとの報告があり[13]，現在研究が行われつつある．いずれの治療法も国内外を通じて実際に治療を受けた症例数が不十分で，効果についての一定の見解はない．

至適治療時期

一般的には発見時に緊急を要することは少ない．治療の適応は大きく機能的問題・整容的問題の2点であり，どちらも許容範囲内であると納得できる軽症の場合，必ずしも治療の必要はない．ただし経過中に内出血や感染などを発症し，疼痛などの症状や外観の変化などの2次症状を生じることがある．これらが誘因となりリンパ管腫が縮小することも知られているが[4]，頻繁におこると不都合も多いので治療適応となりうる．生後1年ぐらいは病変が自然縮小していくこともある．一方，治療にもかかわらず病変が増大することもあり，乳児期に必ずしも急いで治療を開始する必要はない．

ただし，頸部に病変がある場合にはCTなどで病変が咽頭後壁部まで広がっていないことを確認しておく．とくに乳児では，咽頭後壁まで広がる場合には，出血や感染などで容易に上気道閉塞をきたすため，注意が必要である（**図2**）．症状が出たら気道確保が必要となる場合も多く，早期の外科的介入を要することもある．

気道狭窄症状は年齢とともに出にくくなる傾向が認められるため，腫脹を誘発する硬化療法は乳児期には避けることも考慮してよい．

特殊な型のリンパ管腫

他に全身性にリンパ管腫が発生し進行性を認めるリンパ管腫症やさらに骨病変を合併するGorham-Stout症候群，血管奇形と混在するKlippel-Trenauney（-Weber）症候群など，リンパ管腫を含む疾患，症候群があるが非常にまれである．

おわりに

リンパ管腫は比較的まれであるが，診断されれば，小児外科を中心として外科的治療・局所療法にて改善を期待できることが多い．緊急を要することは少ないが，頸部病変の場合に気道狭窄の可能性を念頭におく必要がある．

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◆特集／血管腫・血管奇形治療マニュアル

リンパ管腫(リンパ管奇形)の診断・治療戦略

藤野明浩*

Key Words：リンパ管腫(lymphangioma)，リンパ管奇形(lymphatic malformation)，硬化療法(sclerotherapy)，OK-432，嚢胞性リンパ管腫(cystic lymphangioma，macrocystic lymphatic malformation)，海綿状リンパ管腫(cavernous lymphangioma，microcystic lymphatic malformation)

Abstract　リンパ管腫は主に小児期に発症する腫瘤性病変で，正常組織内に網目状に広がる大小様々なリンパ嚢胞からなる．近年徐々に浸透しつつある脈管病変のISSVA分類においてはリンパ管奇形に分類されている．良性疾患であり，多くは治療にて改善するが，一方で重症・難治性症例が存在し治療に難渋する．診断は主に画像検査によりなされ，治療には主に硬化療法，手術療法が行われる．それぞれに特徴があり，治療を行う際にはその適応，タイミング，治療法の選択，戦略などにつきよく検討することが必要である．

はじめに

リンパ管腫は主に小児期に発症する腫瘤性病変で，正常組織内に網目状に広がる大小様々なリンパ嚢胞からなる．良性疾患であり，多くは治療にて改善するが，一方で重症・難治性症例が存在する．頭頚部に頻発し(40～70%と言われる)，外観上の問題を生じるとともに，巨大な患部の感染や腫瘤内出血による炎症や疼痛，気道周辺病変による気道閉塞などに悩まされる症例が約20%存在する[1]．

リンパ管腫はその病変に細胞増殖性など腫瘍の特性は少なく，また先天性に形成されていることが多いため，一種の発生異常による奇形と捉えることが妥当と考えられ，近年ISSVA(International Society of Studying Vascular Anomaly)分類では，リンパ管奇形(lymphatic malformation)と分類されている(表1)．ただし，このリンパ管奇形の分類の中にはいわゆるリンパ管腫を含む多彩なリンパ管疾患が含まれており，病名としてのリンパ管腫と病態を示すリンパ管奇形は現時点では同義とは言えない．筆者らは今後この領域について検討を進め，臨床経過，画像，病理などの観点からリンパ管疾患の細分化を試みたいと考えている．小文においてはこの疾患を表すのにリンパ管腫を用いることとする．

病　因

病因は明らかにされていない．リンパ管腫は，頚部・腋窩など胎生期にリンパ嚢を形成する部からの発生が多いことや胎生期から病変が認められるという臨床的特徴より，胎生のリンパ管形成時期に何らかの異常を生じ嚢胞性病変を形成する，と言われている[2]が定かでない．発生に関して性差や遺伝性は認められていない[3]．

外科的切除の後などに，明らかに後天性に発生したと考えられる症例もある(特に婦人科領域)．

診　断

リンパ管腫はほとんどの場合，画像検査により診断される．超音波，CT，MRI，いずれも有用で

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