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Congenital lymphangiomatosis: Multidisciplinary approach

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ABSTRACT

Background: Diffuse lymphangiomatosis is a rare disorder of the lymphatic vessels. Its prognosis is poor and its treatment not codified.
Methods: We describe the case of a 14 years old boy known for a lymphatic malformation of the left chest wall with pleuropulmonary, bone and visceral involvement. He presented with respiratory difficulties and a left pleural effusion. The treatment associated thoracic drainage, surgical pleurectomy and iterative sclerotherapy.
Results: The patient is currently asymptomatic. On imaging, there is a decrease of the left lateral thoracic component and a resolution of the intra-pleural portion.
Conclusions: The treatment of diffuse lymphangiomatosis is based on a multimodal management.

1. Introduction

Lymphangiomatosis (LMs) refers to the presence of multiple lymphangiomas in various organs or regions of the body, but most commonly affects the cervicothoracic area [1]. Its clinical expression and prognosis vary greatly, depending mainly on the site and the extent of the disease. The concomitant involvement of bone tissue or of the thoracic system is related to a poor prognosis [2]. A visceral involvement is associated with a high mortality rate [3]. LM is extremely difficult to treat and remains a challenge for clinicians and a trial for children and their families.

This report describes the presence of an extensive LM in a 14 year-old boy, already known as having a left chest wall lymphatic malformation; he arrived at the emergency department with respiratory difficulties and a cervico-mediastinal lymphatic malformation ruptured into the pleural cavity. We describe a successful multi-modality therapeutic approach.

This report has obtained our Institutional Review Board (IRB) approval.

2. Case report

At the age of one year, this patient had been seen for a soft subcutaneous mass involving the anterior left chest wall. The shape of this mass was not altered by a change of position of the patient. The overlying skin was normal. Ultrasound (US) and magnetic resonance imaging (MRI) revealed a multilocular lesion containing multiple septa, located in the axillary fossa and the left lateral chest wall, measuring 9 × 5 cm, associated with an intra-parenchymal four mm cystic lesion of the postero-apical segment of the superior left lobe. Several cystic lesions of the spleen were found, the largest measuring two cm. A cystic lesion on the lower pole of the left kidney and a two mm lesion on the vertebral body of L2 in the lumbar spine were also found. As the patient was otherwise asymptomatic, he was placed under simple observation.

At the age of nine years, the patient presented a gradually enlarging left supraclavicular mass associated with a similar left prepectoral lesion. MRI showed a lymphatic malformation of the left lateral chest wall, extending now into the anterior compartment of the mediastinum and the left cervical stage with ipsilateral dorsal muscle invasion. It also showed a progression of several lower intralobar lesions, evoking pulmonary lymphangiectasis. It also turned out that the pa-

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tient had suffered four fractures at the level of the left clavicle, each time occurring after a commonplace traumatism.

Two years later, the patient arrived at the emergency department with a 1-week history of dyspnea, cough, nocturnal awakenings, apathy, dysphagia and vomiting and weight loss, without fever. He also complained of left cervical, thoracic and mild clavicular pain. X-rays showed a left pleural effusion, resulting in a mediastinal shift. A chest tube was placed in the thoracic cavity, draining a total of 1300 ml of serous-bloody fluid. Initial laboratory results revealed a lymphocyte effusion, predominantly of T lymphocytes.

The evolution was complicated, with sepsis and recurrence of a large left-effusion, and associated with an empyema. Despite adequate antibiotic treatment and pleural drainage, the patient remained highly feverish.

As the non-surgical treatment had failed, decortication was indicated and performed. Through a hemi-clamshell approach, a resection of mediastinal cysts, pulmonary decortication and parietal pleurectomy were performed. The patient also underwent surgical removal of the thymus and a wedge resection of the lower lobe since it was invaded by several cystic structures (Figs. 1 and 2).

Pathological analysis described a diffuse lymphangiectasis, with lesions observed at the pleural, parenchymal and thymic levels associated with mediastinal macrocystic lymphatic malformation consistent with a diffuse pleuroparenchymal lymphangiomatosis (Fig. 3A, B, 4A, 4B).

The postoperative course was uncomplicated and the patient was discharged one month later.

He was readmitted after 15 days for a right chylothorax probably due to a thoracic duct lesion and left pleural septa effusion, both drained.

A second left pulmonary decortication by thoracoscopy and pleurodesis by mechanical pleura-crushing proved necessary as well as three sessions of pulmonary actylise injection. The patient then underwent serial punctures on an outpatient basis because of a persistent left pleural effusion.

A multidisciplinary discussion lead to the decision to carry out a series of sclerotherapies by percutaneous intralesional injection of doxycycline and bleomycin into the pleural cavity, the left clavicle and subclavicular cysts at three months' intervals.

MRI control after three sessions showed a marked decrease of the cystic components of the known left lateral thoracic lymphatic malformation, with a resolution of the left apical intralobar portion and a decrease of the left pectoral component, associated with a stabilization of bone involvement with marked sclerosis of the margins of the clavicle, reflecting an early response to treatment. This treatment achieved a reduction of approximately 90% of the volume of the macrocysts and chylothorax. (Figs. 5 and 6).

MRI performed one year later showed the same results and the stabilization of the lesions.

The patient reported a significant improvement of his clinical condition, the disappearance of pain, his resumption of sport activities without dyspnea and no new fractures of his left clavicle.

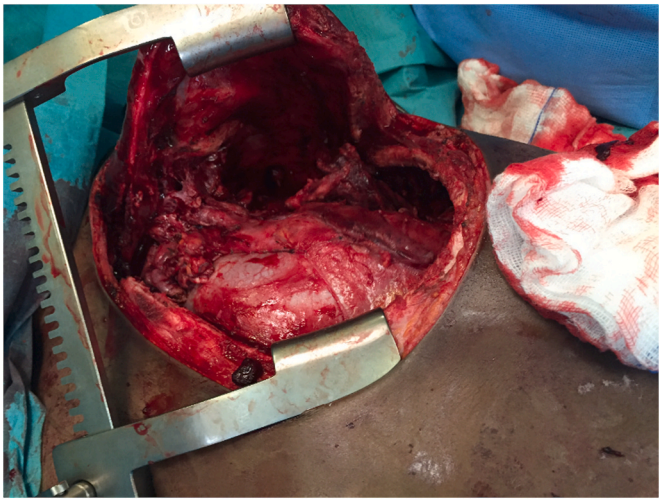

Fig. 1. Left pulmonary lobe, peroperative aspect.

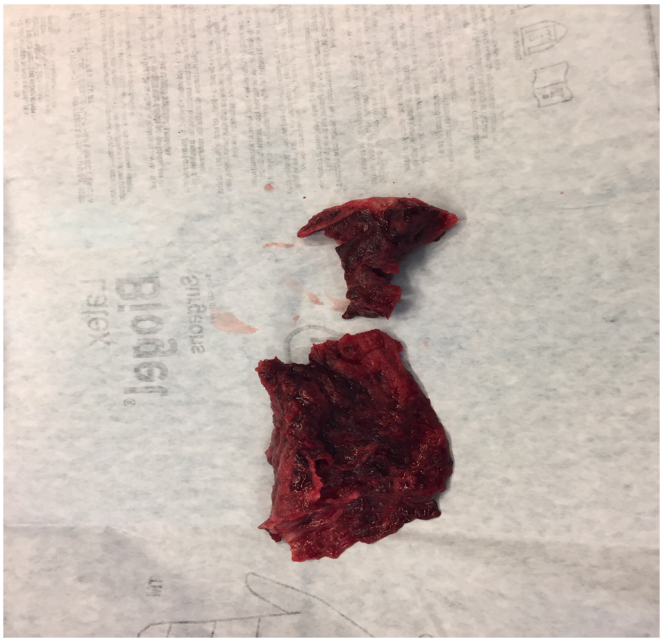

Fig. 2. Parietal pleura: Thickened and cystic macroscopic aspect.

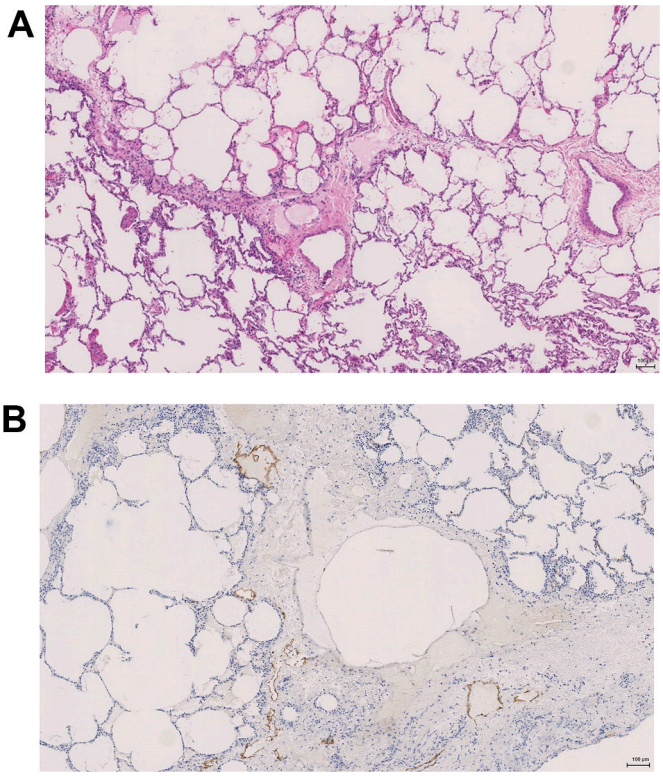

Fig. 3. Left pulmonary lobe, surgical biopsy
A Small ectatic vessels disposed along the interlobular septaB The D2.40 staining highlights increased numbers of small lymphatic vessels in the interlobular septa.

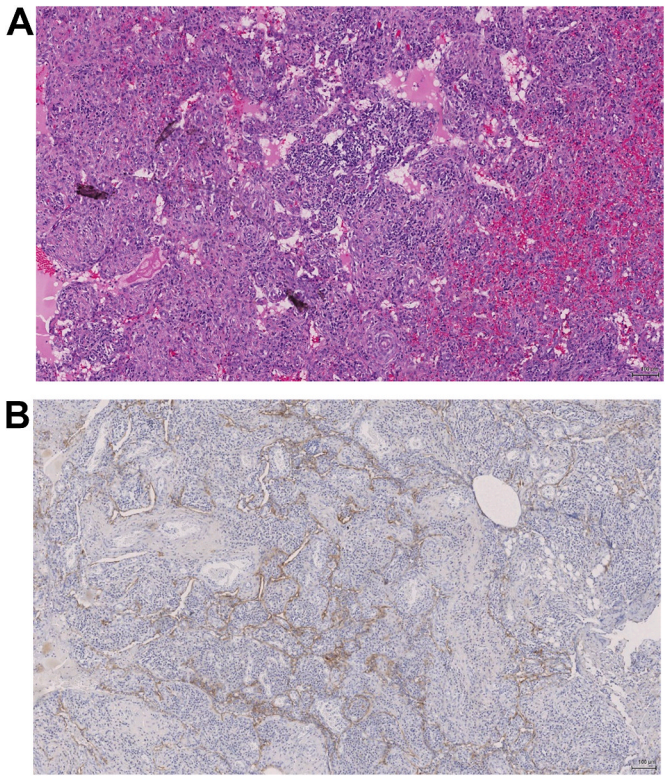

Fig. 4. Pleural biopsy
A A dense anastomosing network of dissecting channels with associated chronic inflammation.B The D2.40 staining confirms the lymphatic nature of the dissecting vessels.

Finally, an immunological assessment at three months after thymectomy revealed a lymphopenia, particularly concerning the CD4 level with insufficient vaccine response for diphtheria and a low response against tetanus and pneumococcus. *TENs (recent emigrant moods*) were also low. A reinjection of Infanrix Hexa ® and Prevenar ® was done during the last hospitalization. Antibioprophylaxis with Bactrim three times a week was started.

3. Discussion

LMs are benign slow flow vascular malformations resulting in a proliferation of nonfunctional lymphatic tissue that may involve any part of the body. They can be caused by a congenital defect of lymphatic development or by a mechanical obstruction of normal lymphatic vessels. Their incidence in the pediatric population amounts to one new case per 12000 birth [4,5].

Most LMs are diagnosed in the first two years of life, but some can also be diagnosed at any age. Antenatal diagnosis is possible between the 15th and 22nd week of gestation thanks to the routine use of prenatal ultrasound screening [6].

Almost 30% of LMs are found in the cervical region, 20% in the head, 10% in the trunk, and 5% in the anterior chest wall and the axillary cavity. Mediastinum localization represents 1% of all cases [7]. Intrapulmonary lesions are less common [8].

LMs are classified according to their size as microcystic (less than two cm), macrocystic (greater than two cm), or mixed. Macrocystic LMs can have septa resulting in a total obstruction of the primitive lymphatic sacs, or may be non-septated due to a partial obstruction [9].

On physical examination, macrocystic lesions are solitary soft subcutaneous masses with normal overlying skin. On ultrasound, they are compressible, anechoic cysts with specific thin septations and without

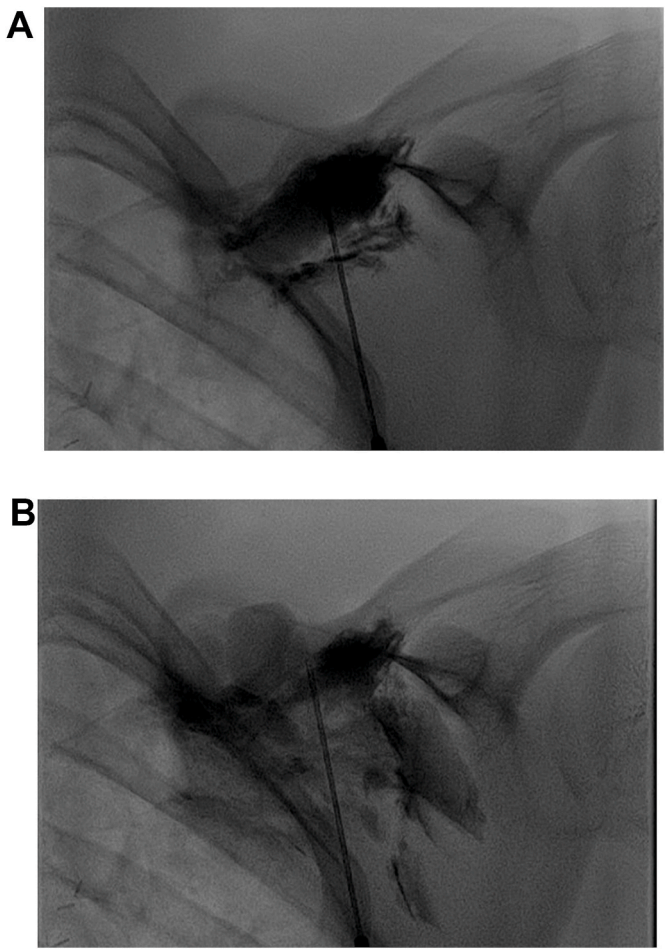

Fig. 5. First sclerotherapy session
AP plain radiography during the first sclerotherapy session with doxycycline injection into the clavicle (A & B) with a 19 gauge needle and bleomycin injection into the pleural cavity (C) with a 5F sheath catheter. Note the diffusion of the doxycycline through the cortical of the bone with progressive filling of the macro cysts in the vicinity (B).

Doppler flow. Microcystic lesions usually appear as vesicles filled with lymphatic fluid. They present as tiny cavities of solid appearance and are hyperechoic [10]. The imaging assessment is essentially based on ultrasound and MRI that allow a complete evaluation of the extent of the disease without the need of ionising radiation.

LM is characterised by the presence of multiple lymphangiomas [11]. It is frequently associated with other lymphatic related abnormalities and involves multiple organs in 75% of cases. It is a rare disorder, most frequently present in late childhood without sex predilection [12]. LM lesions can occur in any tissue in which lymphatics are normally found, with a preference for thoracic and neck involvement. Up to 75% of patients with LM have bone involvement. Single or multiple effects of LM can be found within the mediastinum, adherent to the pleura, or within the chest wall [4]. Thoracic lesions may present as chylothorax and/or chylopericardium (49%), as a mass (47%), as pulmonary infiltrates (45%). Extra-thoracic lesions may present as bone lesions (39%), as splenic lesions (19%), as cervical lymphadenopathy (15%), as disseminated intravascular coagulation (9%), and as skin manifestations (7%) [13,14].

The first clinical sign of LM is generally a superficial soft tissue lesion. Other signs may then appear, including respiratory symptoms, chest pain, abdominal or neck swelling, and pathological fractures [2].

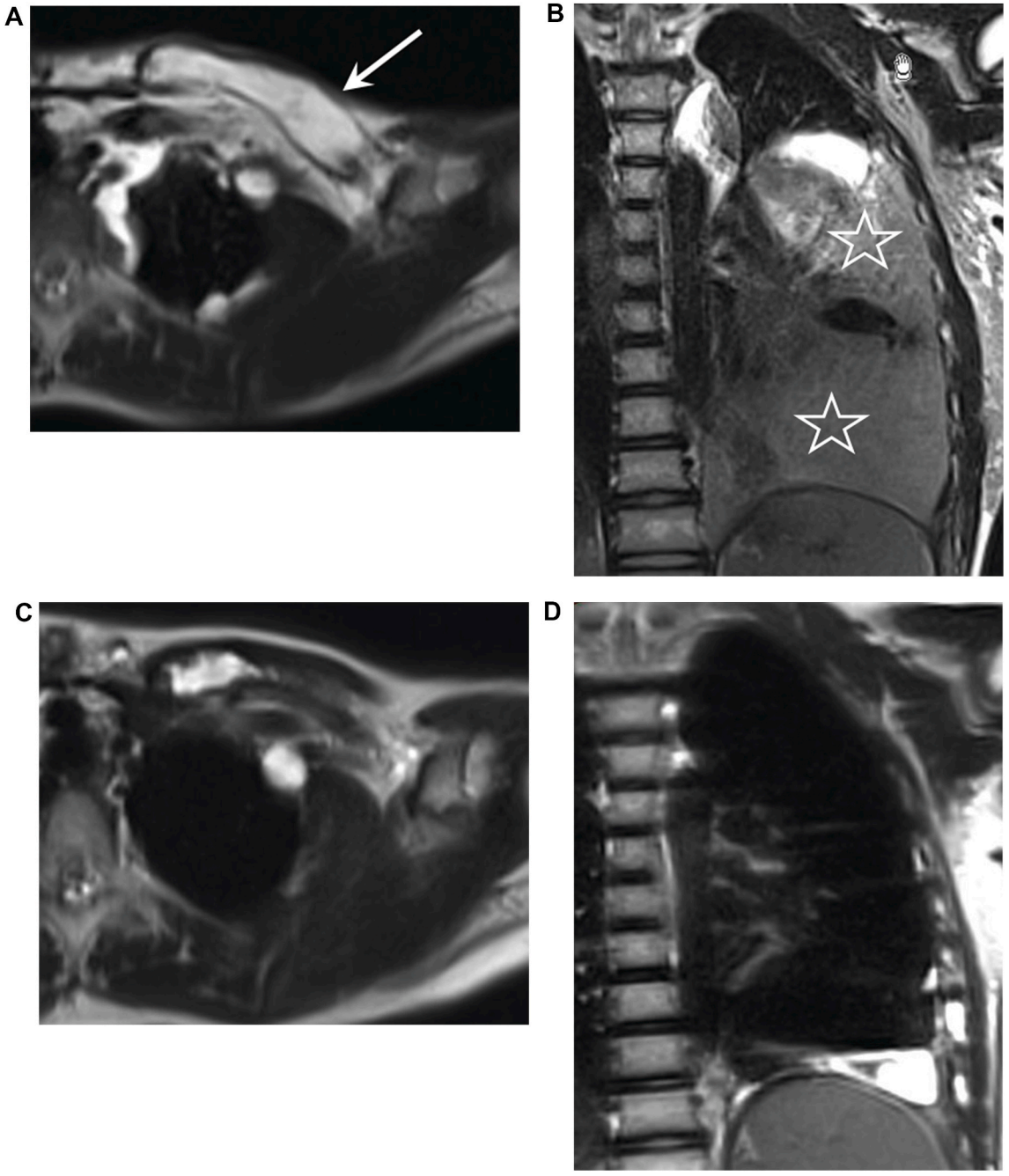

Fig. 6. Evolution of lymphatic lesions before and after sclerotherapy on magnetic resonance imaging (MRI).
MRI in T2SE weighted sequences performed before sclerotherapy in November 2017 (A, & B), then after the third session in January 2019 (C & D. Bone remodeling with progressive disappearance of the macro cysts of the clavicle and sclerotic reaction. Dramatic shrinkage of the chylothorax up to a limited remaining collection.

Pulmonary LM can also be suspected in the presence of progressive growth and compression of adjacent structures. But this is a rare diagnosis and only few cases are published in the literature [15].

The indication for treatment is based on the age of the patient, the site, size and type of the lesion, and on functional symptoms such as swelling, bleeding, recurrent infection, dysphagia, respiratory distress or cosmetic deformity. Severe forms may require treatment based on sclerotherapy or surgical resection.

Percutaneous sclerotherapy is considered the first-line treatment of LM, and is more successful in cases of macrocystic LMs. Many agents are used, such as doxycyclin, bleomycin, absolute ethanol, betadine, OK-432 (lyophilized Streptococcus) and alcoholic zinc solution. Under imaging guidance, the sclerosant agent is injected by direct approach after decompression of the cyst. The aim is to induce an inflammatory reaction in the endothelium of the lymph-vessel, resulting in the reduction of its size. This procedure is generally performed under general anesthesia. Complications include local extravasation, skin necrosis, cellulitis and compression of nearby structures such as airways and nerves [16,17]. Sclerotherapy probably carries less risk than surgery. Complete excision is often challenging due to the risk of iatrogenic injury to adjacent structures [18], bleeding, and the inability to separate lymph collections from normal structure, leading to high rates of recurrence [19]. The surgical approach is reserved for severe

lymphatic disorders unresponsive to other therapies, but is still associated to a high rate of recurrence.

In general practice, no single modality of treatment is effective and multi-modal therapy is often necessary, especially in patients with widespread disease and for whom therapeutic options are often palliative.

Recently, mTOR inhibitors showed promising results in the management of vascular anomalies. mTOR is a serine threonine kinase regulated by phosphoinositide 3 kinase (PI3K) and protein kinase B (Akt). The PI3K/Akt/mTOR pathway is the basis for cell growth and proliferation; it also increases the expression of the vascular endothelial growth factor (VEGF) regulating angiogenesis and lymphangiogenesis. mTOR inhibitors directly inhibit mTOR, blocking downstream protein synthesis and presenting antitumoral and antiangiogenic effect. Rapamycin (sirolimus ®) is one of the best known mTOR inhibitors. Resistant complex lymphatic anomalies with visceral and bony adverse effects have shown good response to sirolimus ® [20,21].

4. Conclusion

LM is a rare vascular malformation in children and has varying clinical presentations. The radiological study confirms the diagnosis and allows the assessment of the extent of the lesions. Literature on the subject is limited, and the treatment is often poorly coded.

In cases of inoperable and diffuse forms, sclerotherapy may be mandatory and should be discussed as the first line treatment, as we learned in this particular case.

Patient consent

Consent to publish the case report was obtained.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Timke C, Krause MF, Oppermann HC, Leuschner I, Claviez A. Interferon alpha 2b treatment in an eleven-year-old boy with disseminated lymphangiomatosis. Pediatr Blood Canc 2007;48:108–11.
[2] Wong C, Chu T. Clinical and radiological features of generalised lymphangiomatosis. Hong Kong Med J 2008;14(5):402–4.
[3] Olmos M, Fern MA, Fern M, Landeras R. Disseminated bone lymphangiomatosis. Eur J Radiol 2007;64:103–6.
[4] Faul JL, Berry GJ, Colby TV, et al. Thoracic lymphangiomas, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. Am J Respir Crit Care Med 2000;161:1037–46.
[5] Benninghoff MG, Todd WV, Bascom R. Incidental pleural-based pulmonary lymphangioma. J Am Osteopath Assoc 2008;108(9):525–8.
[6] Goldstein I, Leibovitz Z, Noi-Nizri M. Prenatal diagnosis of fetal chest lymphangioma. J Ultrasound Med 2006;25(11):1437–40.
[7] Hancock BJ, St-Vil D, Luks FL, Di Lorenzo M, Blanchard H. Complications of lymphangiomas in children. J Pediatr Surg 1992;27(2):220–4.
[8] Lee CH, Kim YD, Kim K, et al. Intrapulmonary cystic lymphangioma in a 2-month-old infant. J Kor Med Sci 2004;19:458–61.
[9] Bianca S, Bartoloni G, Boemi G, et al. Familial nuchal cystic hygroma without fetal effects: genetic counselling and further evidence for an autosomal recessive subtype". Congenital Anom 2010;50(2):139–40.
[10] Alfageme Roldán F, Salgüero Fernández I, Zamanta Munoz Garza I, Roustán Gullóna G. Update on the use of ultrasound in vascular anomalies. Actas Dermosifiliogr 2016;107(4):284–93.
[11] Canny GJ, Cutz E, MacLusky Ib I, Levison H. Diffuse pulmonary angiomatosis. Thorax 1991;46:851–3.
[12] Kransdorf MJ. Benign soft tissue tumors in a large referral population: distribution of specific diagnoses by age, sex, and location. AJR 1994;164:395–402.
[13] Alvarez OA, Kjellin I, Zuppan CW. Thoracic lymphangiomatosis in a child. J Pediatr Hematol Oncol 2004;26:136–41.
[14] Steiner GM, Farman J, Lawson JP. Lymphangiomatosis of bone. Radiology 1969;93:1093–8.
[15] Tazelaar HD, Kerr D, Yousem SA, Saldana MJ, Langston C, Colby TV. Diffuse pulmonary lymphangiomatosis. Hum Pathol 1993;24:1313–22.
[16] Lerata J, Mounayerb C, Scomparina A, Orsela S, Bessedea JP, Aubrya K. Head and neck lymphatic malformation and treatment: clinical study of 23 cases. Eur Annal Otorhinolaryngol Head Neck Dis 2016;133:393–6.
[17] Alomari AI, Karian VE, Lord DJ, et al. Percutaneous sclerotherapy for lymphatic malformations: a retrospective analysis of patient- evaluated improvement. J Vasc Intervent Radiol 2006;17:1639–48.
[18] Olímpio Hde O, Bustorff-Silva J, Oliveira Filho AG, Araujo KC. Cross-sectional study comparing different therapeutic modalities for cystic lymphangiomas in children. Clinics 2014;69:505–8.
[19] Dunkelman H, Sharief N, Berman L, Ninan T. Generalised lymphangiomatosis with chylothorax. Arch Dis Child 1989;64:1058–60.
[20] Triana P, Dore M, Nuñez Cerezo V, et al. Sirolimus in the treatment of vascular anomalies. Eur J Pediatr Surg 2017;27:86–90.
[21] Reinglas J, Ramphal R, Bromwich M. The successful management of diffuse lymphangiomatosis using sirolimus: a case report. Laryngoscope 2011;121:1851–4.