

# The use of sirolimus in the treatment of giant cystic lymphangioma

## Four case reports and update of medical therapy

Ilaria Amodeo, MD<sup>a</sup>, Mariarosa Colnaghi, MD<sup>a</sup>, Genny Raffaelli, MD<sup>a</sup>, Giacomo Cavallaro, MD<sup>a,\*</sup>, Fabrizio Ciralli, MD<sup>a</sup>, Silvana Gangi, MD<sup>a</sup>, Ernesto Leva, MD<sup>b</sup>, Lorenzo Pignataro, MD<sup>c</sup>, Irene Borzani, MD<sup>d</sup>, Lorenza Pugni, MD<sup>a</sup>, Fabio Mosca, MD<sup>a</sup>

### Abstract

**Rationale:** Lymphatic malformations (LMs) are rare and benign anomalies resulting from the defective embryological development of the primordial lymphatic structures. Due to their permeative growth throughout all tissue layers, treatment is often challenging. Small asymptomatic lesions can be conservatively managed, while symptomatic lesions require active management. Surgery has been historically considered the treatment of choice, but today less invasive therapeutic options are preferred (sclerotherapy, laser therapy, oral medications). However, there are not uniform therapeutic protocols. Sirolimus is an oral medication that has been reported to be effective in the recent literature. Here we present the case of 4 newborns with giant multicystic lymphangioma treated with oral sirolimus after surgical resection had failed.

**Patient concerns:** At birth the LMs were clinically appreciated as giant masses involving different organs and structures.

**Diagnoses:** All patients had a prenatal diagnosis of giant multicystic lymphangioma confirmed at histological and cytological analysis.

**Interventions:** Patients were treated with oral sirolimus after unsuccessful surgical resection.

**Outcomes:** In all patients, sirolimus determined an overall reduction of the mass and a global involution from the macro- to the microcystic composition. Sirolimus was safe and poor disadvantages had been observed. The main and isolated adverse effect at laboratory analysis was progressive dyslipidemia, with increasing levels of total cholesterol and triglycerides.

**Lessons:** To date, our experience with sirolimus in the management of LMs is favorable. We recommend the use of sirolimus after unsuccessful surgical excision have been tried or when the surgical approach is not feasible. A multidisciplinary follow-up is needed to monitor disease evolution.

**Abbreviations:** DOL = day of life, EXIT = ex utero intrapartum treatment, LMs = lymphatic malformations, MRI = magnetic resonance imaging.

**Keywords:** cystic lymphangioma, lymphangiomatosis, lymphatic abnormalities, neonate, sirolimus

## 1. Introduction

Lymphatic malformations (LMs), traditionally called lymphangiomas, are rare and benign anomalies resulting from the defective embryological development of the primordial lymphatic structures.

Editor: María-Luz Couce.

Author contributions: IA, GC, and GR, conceived and wrote the manuscript; all authors contributed to the revision of the manuscript and approved the final draft.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Neonatal Intensive Care Unit, <sup>b</sup> Department of Pediatric Surgery, <sup>c</sup> Department of Otolaryngology, <sup>d</sup> Pediatric Radiology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy.

\* Correspondence: Giacomo Cavallaro, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via Della Commenda 12, 20122 Milano, Italy (e-mail: giacomo.cavallaro@mangiagalli.it).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2017) 96:51(e8871)

Received: 30 April 2017 / Received in final form: 28 October 2017 / Accepted: 4 November 2017

<http://dx.doi.org/10.1097/MD.0000000000008871>

They consist of dilated lymphatic channels forming multiple cysts of variable size (macro- or microcystic lymphangioma).<sup>[1,2]</sup>

Due to their permeative growth throughout all tissue layers, treatment is often challenging. Surgical excision has been historically considered the treatment of choice, but today less invasive therapeutic options are preferred. Sirolimus is an oral medication that has been reported to be effective in the recent literature.<sup>[2,3]</sup>

Sirolimus (rapamycin) is an immunosuppressive and antitumor agent which belongs to the mammalian target of rapamycin (mTOR) inhibitors group. The mTOR/PI3K pathway has been demonstrated to be involved in vascular development. Activation of mTOR signaling increases the expression of vascular endothelial growth factor A and C (VEGF-A and VEGF-C), key regulators of angiogenesis and lymphangiogenesis respectively, promoting cell growth and vascular proliferation. Sirolimus can inhibit abnormal vascular proliferation by blocking the mTOR/PI3K pathway and by reducing the production of VEGF and responsiveness of its receptors.<sup>[4-9]</sup> Its most significant adverse effects are thrombocytopenia, rash, asthenia, nausea, edema, anorexia, anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia. Rare but potentially serious side effects associated with the use of sirolimus have also been described, such as infections and cardiac disorders.<sup>[10,11]</sup>

**Table 1**

**Patients characteristics.**

	Case 1	Case 2	Case 3	Case 4
<b>History</b>				
Prenatal diagnosis	Multicystic lymphangioma	Multicystic lymphangioma	Multicystic lymphangioma	Multicystic lymphangioma
Prenatal complications	—	Airways compression	Airways compression, hydrothorax	Airways compression
Delivery location	Inborn	Inborn	Inborn	Inborn
Delivery mode	CS + EXIT	CS + EXIT	CS + EXIT	CS + EXIT
Nationality of parents	Tunisia	Italy	Italy	Italy
Sex	Male	Male	Male	Female
Gestational age	36 wk + 3 d	35 wk + 6 d	35 wk	38 wk + 3 d
Birth weight	3825 g	3060 g	2750 g	3370 g
APGAR 1'/5'	8/10	7/7	2/8	6/7
Days of MV	1	42	22	62
Days of NIV	0	0	10	2
<b>Clinical findings</b>				
Physical examination	Left posterior hemithorax and right gluteus mass, bluish discoloration of the skin	Left cervical mass, bluish discoloration of the skin	Left cervical mass, normal skin	Left cervical mass, normal skin
Radiological findings	US and MRI with contrast: multicystic lymphangioma	US and MRI with contrast: multicystic lymphangioma	US and MRI with contrast: multicystic lymphangioma	US and MRI with contrast: multicystic lymphangioma
Localization	Thorax, abdomen (intra- and retroperitoneal extension)	Face, neck, thorax (upper mediastinum, left supraclavicular region)	Neck, thorax (upper mediastinum)	Neck, thorax (upper mediastinum, left supraclavicular region)
Organs involved in the diagnosis	Inferior vena cava, aorta, right renal artery, iliac arteries, right kidney, liver	Cervical muscles, tongue basis, trachea, larynx	Cervical muscles, vascular nervous fascia, retropharyngeal space, trachea, larynx	Cervical muscles, vascular nervous fascia, retropharyngeal space, trachea, larynx, thymus, thoracic arteries, superior vena cava, heart
Maximum diameter of the cysts	4 cm	5 cm	3 cm	3 cm
Complications	Intracystic bleeding	Intracystic bleeding, airways obstruction	Airways obstruction	Intracystic bleeding, airway obstruction, heart displacement
Tumor markers	Not relevant	Not relevant	Not relevant	Not relevant
Blood routine analysis	Not relevant	Not relevant	Not relevant	Not relevant
<b>Surgical treatment</b>				
Time of intervention	2 mo of life	10 d of life	2 wk of life	2 mo of life
Surgery	Drainage of cyst liquid	Surgical resection	Surgical resection	Surgical resection
Histology/cytology	Fibrin, lymphocytes, histiocytes, RBCs, no tumor cells	Cystic lymphangioma	Cystic lymphangioma	Cystic lymphangioma
Results	Partial reduction of mass extension	Partial reduction of mass extension	Partial reduction of mass extension	Partial reduction of mass extension
Complications	No	Facial palsy	No	No
Relapse	No	Yes	Yes	No
Time of relapse	—	3 wk after	18 mo after	—
Characteristics	—	New cysts from the residual lymphangioma	New cysts from the residual lymphangioma, diffuse lymphangiomatosis	—
<b>Other treatments</b>				
Laser therapy	No	Yes	No	No
Tracheostomy	No	Yes	No	No
Other	—	CO <sub>2</sub> laser	Thoracic drainage	First sirolimus treatment for 5 wk before surgical intervention. Fluctuating blood levels, no clinical improvement
<b>Sirolimus treatment</b>				
Time of intervention	3 mo of age	16 mo of age	23 mo of age	2.5 mo of age
Dosage	0.4–0.8 mg/m <sup>2</sup> 2 times/d	0.4–0.8 mg/m <sup>2</sup> 2 times/d	0.4–0.8 mg/m <sup>2</sup> 2 times/d	0.4–0.8 mg/m <sup>2</sup> 2 times/d
Clinical findings	Reduction of mass size	Reduction of mass size	Reduction of mass size	Reduction of mass size
Radiological findings	MRI with contrast: reduction of mass size, prevalence of microcystic elements	MRI with contrast will be soon performed	MRI with contrast: reduction of mass size, prevalence of microcystic elements	MRI with contrast: reduction of mass size, prevalence of microcystic elements
<b>Averse effects</b>				
Anemia	No	No	No	No
Leucopenia	No	No	No	No
Thrombocytopenia	No	No	No	No
Dyselectrolytemia	No	No	No	No
Renal failure	No	No	No	No
Dyslipidemia	Yes	No	Yes	Yes
Fever	No	No	No	No
Infections/sepsis	No	No	No	No
Rash	No	No	No	No
Hypotension	No	No	No	No
Hypertension	No	No	No	No
Gastrointestinal symptoms	No	No	No	No
Other	No	No	No	No
Ongoing treatment	Yes	Yes	Yes	Yes

CS = cesarean section, EXIT = ex utero intrapartum treatment, MRI = magnetic resonance imaging, MV = mechanical ventilation, NIV = noninvasive ventilation, RBCs = red blood cells, US = ultrasound.

We present the cases of 4 newborns with giant multicystic lymphangioma treated with oral sirolimus after surgical resection had failed. The characteristics of the 4 newborns are summarized in Table 1. The diagnosis and treatment of all cases were performed in the Neonatal Intensive Care Unit of Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico (Milan, Italy) from 2014.

## 2. Case reports

### 2.1. Case 1

A male baby was born by cesarean section for labor starting at 36 weeks of gestation. The lesion was first detected at the prenatal ultrasound. The mass extended from the posterior area of the neck to the lower abdomen but did not seem to determine airways obstruction. At birth ex utero intrapartum treatment (EXIT) was performed, with no complications. APGAR score was 8/10 and birth weight 3825 g. At physical examination, a purple vascular mass involving the left posterior hemithorax and the right gluteus was present. Magnetic resonance imaging (MRI) scan with contrast showed thoracic and abdominal cystic formations with corpuscular content, which infiltrated the thoracic and the abdominal wall, including the diaphragm. Lesions involved multiple vessels and organs (inferior vena cava, aorta, right renal artery, iliac arteries, right kidney, liver), reached the right inguinal area and also had a retroperitoneal extension. All MRI scan characteristics confirmed the diagnosis of multicystic lymphangioma (Fig. 1A). Blood analyses were normal, and the principal tumor markers were not relevant. Since the mass did not determine airways obstruction, no surgical intervention was made until the age of 2 months. During the procedure, a big cyst localized in the left hemithorax was drained. At MRI scan with contrast performed 1 month after surgical drainage, the left part of the lymphangioma was reduced in volume, but the rest of the mass was unchanged (Fig. 1B).

At 3 months of age, given the persistence of multiple lesions and the risk of further growth, pharmacological therapy with sirolimus was started. The dosage was 0.4 to 0.8 mg/m<sup>2</sup> 2 times/day, adjusted to maintain sirolimus blood levels between 10 and 15 ng/mL. After 3 months of treatment, an MRI scan with contrast was performed, which documented a significant reduction in mass size and a global involution of the cysts to microcystic or stromal elements (Fig. 1C). Then, a clinical, radiological, and pharmacological follow-up was started, which documented a progressive improvement. The only adverse effect observed was moderate dyslipidemia with high levels of

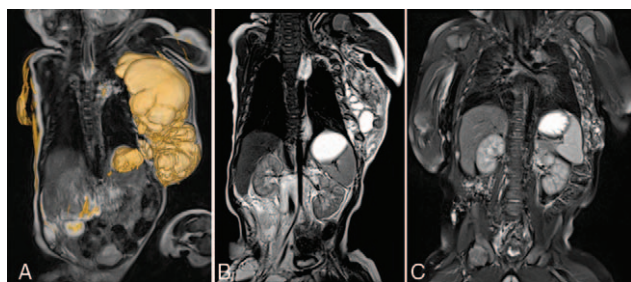
cholesterol and triglycerides started after 6 months of treatment. The patient is currently on clinical, pharmacological, and radiological follow-up and the treatment is still ongoing.

### 2.2. Case 2

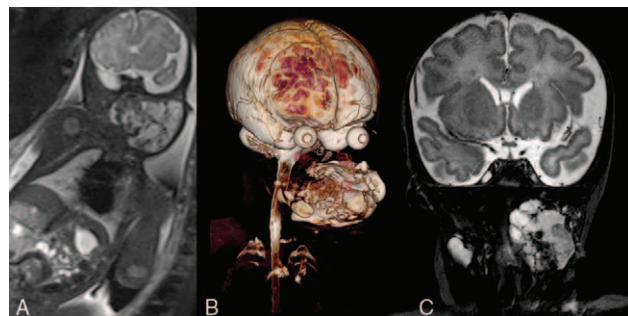
A male baby was born by cesarean section at 35+6 weeks of gestation. A fetal ultrasound performed at 31 weeks of gestation showed the presence of a left cervicofacial mass. Fetal MRI scan confirmed the diagnosis of giant multicystic lymphangioma displacing the trachea and the larynx (Fig. 2A). Therefore, EXIT was performed at birth, and the patient was maintained on mechanical ventilation for the next 6 weeks. APGAR score was 7/7 and birth weight was 3060 g. At physical examination, a big vascular mass was appreciated in the left cervical region. On days of life (DOL) 1, an MRI scan with contrast showed a multicameral mass in the left cervical region. It developed among muscular planes, reached the root of the tongue and infiltrated the deep tissues near the trachea and the larynx. The trachea was displaced contralaterally (Fig. 2B). Blood analyses were normal, and the principal tumor markers were not relevant. On DOL 10, the patient underwent a surgical intervention, although a complete resection was not possible. Intraoperative biopsy confirmed the diagnosis of multicystic lymphangioma. Three weeks after, the MRI scan with contrast showed new cystic formations on the root of the tongue, in the retropharyngeal space and on the mucosal surface of the larynx (Fig. 2C). The laryngeal relapse was treated with CO<sub>2</sub> laser, obtaining a good canalization of the airways. At 6 months of life, due to the progressive growth of the lesions, a tracheostomy became necessary. In consideration of the relapsing course and the diffuse localization, at 16 months of age pharmacological therapy with sirolimus was started. The dosage was 0.4 to 0.8 mg/m<sup>2</sup> 2 times/day with sirolimus blood levels to be maintained between 10 and 15 ng/mL. Despite a gradual increase of the dosage, there were difficulties with maintaining blood concentrations in the therapeutic range, and they were often underdosed (<10 ng/mL). No alterations of routine blood analysis have been observed. The patient is currently on clinical, pharmacological, and radiological follow-up and the treatment is still ongoing.

### 2.3. Case 3

At 29 weeks of gestational age, a multicystic mass of 4.8 cm × 3.8 cm in the left cervical and upper mediastinal region was detected at the fetal ultrasound. During the following weeks of gestation,

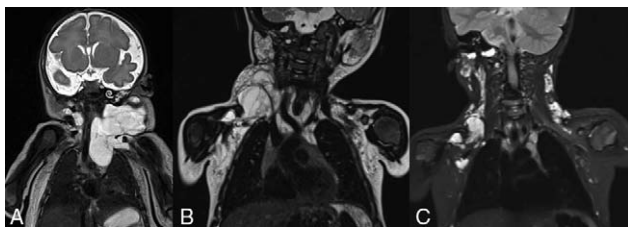


**Figure 1.** T2-weighted MR images performed at different times. Thoracic and abdominal cysts, with retroperitoneal extension, which were present at birth (A). The overall size was 6 cm × 12 cm, with the bigger elements of about 4 cm in diameter. MR image performed after surgical drainage demonstrate that the bigger cyst was reduced in diameter, but the rest of the mass was unchanged (B). After 3 months of sirolimus treatment, a significant reduction in mass size and a global involution of the cysts was obtained (C).



**Figure 2.** Fetal MRI image shows the presence of giant cervical multicystic lymphangioma (A). 3D reconstruction MRI performed at birth showed several cystic elements infiltrating the root of the tongue and the deep tissues near the trachea and the larynx. The maximum diameter was 4 cm (B). Three weeks after surgical resection, new cystic formations appeared in the cervical region (C).

the mass progressively enlarged and the fetus developed left hydrothorax, with compression on airways and displacement of the trachea. For these reasons, this male baby was born by urgent cesarean section and EXIT at 35 weeks of gestational age. APGAR score was 2/8. Birth weight was 2750g. Immediately after birth, hydrothorax was drained, and a thoracic catheter was left in situ for 26 days. The patient was maintained on mechanical ventilation for 22 days and then on noninvasive ventilation for 10 days. At physical examination, a significant mass was appreciated in the left cervical region. At MRI scan performed at DOL 6, several lacunas were observed in the left cervical region, involving the retropharyngeal space and displacing the trachea and the larynx contralaterally. The mass occupied the mediastinum until the carina. The sternocleidomastoideus muscle and the vascular nervous fascia of the neck were infiltrated and compressed (Fig. 3A). Blood analysis was normal, and the principal tumor markers were not relevant. At 2 weeks of life, given the compression of vital structures, surgery was performed, but complete resection was not possible (Fig. 3A). Biopsies confirmed the diagnosis of multicystic lymphangioma. A clinical, pharmacological, and radiological follow-up was started. Eighteen months later, the MRI documented a relapse of the lymphangioma (Fig. 3B). The spleen appeared enlarged and completely infiltrated by millimetric cysts. Moreover, the presence of multiple focal hyperintense anomalies in bone, with no associated edema, was detected for the first time. These anomalies involved different skeletal segments (humerus bones, scapulae, dorsal vertebrae, some ribs, sphenoid, maxilla). In consideration of the continuous evolution and the multiple bone involvement, neither surgical resection nor sclerotherapy were feasible. Then, at 23 months of age pharmacological therapy with sirolimus was started. The dosage was 0.4 to 0.8 mg/m<sup>2</sup> 2 times/day. The desired blood levels were between 10 and 15 ng/mL. A clinical, pharmacological, and radiological follow-up was then started. Despite good compliance, there were difficulties with maintaining blood levels in the therapeutic range and they were often underdosed. At the MRI scan with contrast performed after 6 months of treatment, an overall reduction of the cysts and the spleen diameter was appreciated (Fig. 3C). Bone involvement was essentially stable, with no further progression. After 6 months of treatment with sirolimus, the patient developed mild dyslipidemia with high levels of cholesterol and triglycerides. The patient is currently on clinical, pharmacological, and radiological follow-up and the treatment is still ongoing.



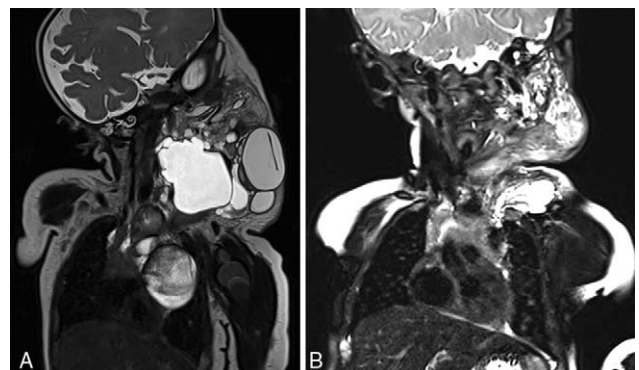
**Figure 3.** T2-weighted MR images performed at different times. At 6 days of life, several cysts were present in the left cervical region, involving the retropharyngeal space and displacing the trachea and the larynx contralaterally. The mass involved the sternocleidomastoideus muscle and the vascular nervous fascia of the neck and occupied the mediastinum until the carina (A). Eighteen months after surgery, a relapse of the lymphangioma was documented in the right supraclavicular region. The presence of multiple anomalies in bone signal was detected for the first time (B). After 6 months of sirolimus treatment, an overall reduction of the cysts was appreciated, while bone involvement was essentially stable (C).

#### 2.4. Case 4

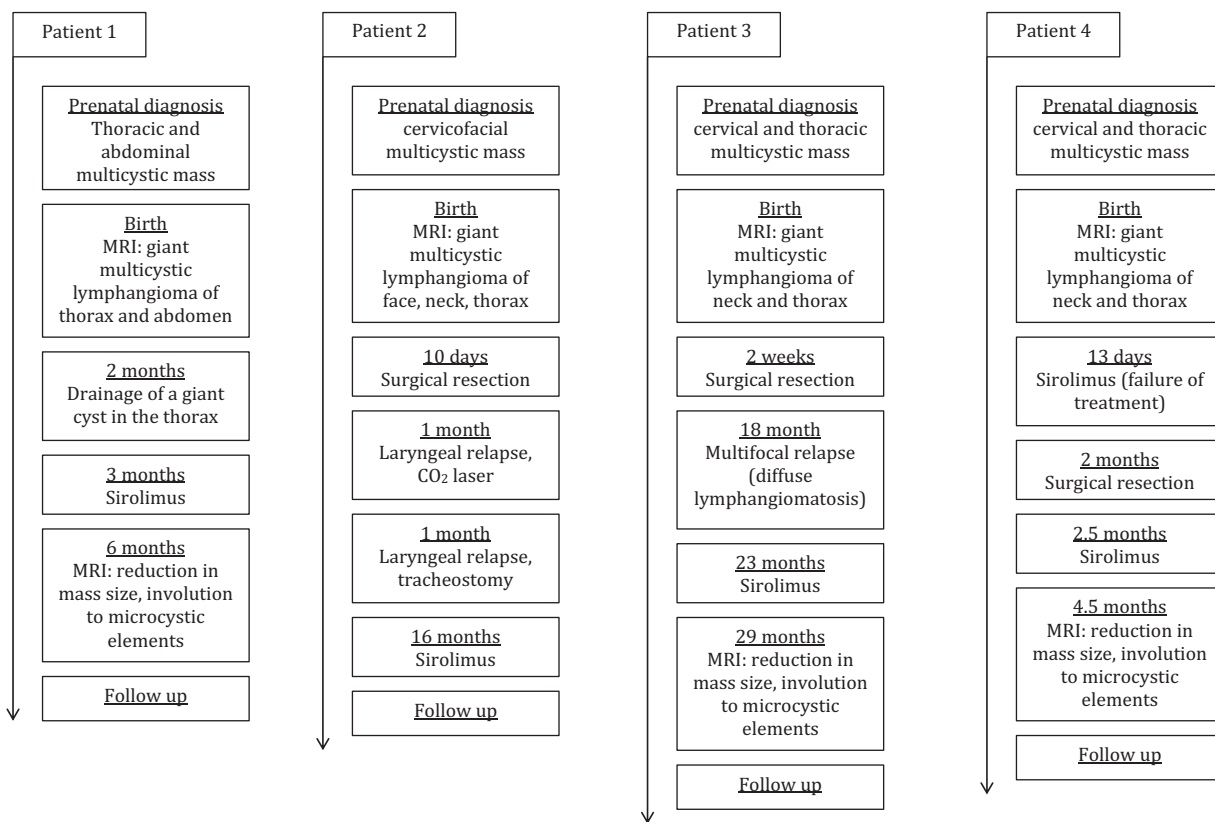
A female baby was delivered by an elective cesarean section with EXIT procedure at 38 weeks+3 days of gestational age after a multicystic LM had been diagnosed at the fetal ultrasound. Birth weight was 3370g, and APGAR score was 6/7. The patient was maintained on mechanical ventilation for 62 days after birth. At physical examination, a big soft mass was appreciated in the left cervical region and the upper portion of the left anterior thorax. On DOL 7, an MRI scan with contrast was performed. The mass originated in the left cervical area and infiltrated several structures (left sternocleidomastoideus muscle, left vascular nervous fascia, occipital muscles, larynx, pharynx). Cysts were in contact with the posterior trachea, thoracic arteries, superior vena cava, and thymus. The mediastinal mass slightly displaced the heart, but no significant compression on the great vessels was detected (Fig. 4A). Given the broad distribution of the cysts and the high probability of surgical failure, treatment with sirolimus was started on DOL 13. Due to the difficulties with maintaining the desirable sirolimus levels, therapy was often discontinued, and no clinical improvement was obtained. For this reason, the patient underwent a partial resection of the mass at 2 months old. Biopsies confirmed the diagnosis of multicystic lymphangioma. After surgery, a consistent reduction in the mass size was appreciated, enabling the mechanical ventilation to be suspended. Two weeks after surgery sirolimus therapy was restarted. The dosage was 0.4 to 0.8 mg/m<sup>2</sup> 2 times/day, calculated to maintain sirolimus blood levels between 10 and 15 ng/mL. A progressive reduction and stabilization of the mass were clinically observed. After 2 months of treatment, the MRI scan with contrast documented an overall involution to microcystic lesions (Fig. 4B). As the isolated adverse effect of sirolimus treatment, the patient developed mild dyslipidemia with high levels of cholesterol. The patient is currently on clinical, pharmacological, and radiological follow-up and the treatment is still ongoing.

#### 2.5. Timeline

Figure 5 summarizes the main clinical and radiologic findings in our patients, which led to the diagnosis of giant cystic lymphangioma, and the major steps in the management and follow-up.



**Figure 4.** T2-weighted MR images performed at different times. At birth a giant lymphangioma was present in the left cervical area and mediastinum, infiltrating several structures (left sternocleidomastoideus muscle, left vascular nervous fascia, occipital muscles, larynx, pharynx). Airways were displaced (A). After a first surgical approach and 2 months of sirolimus treatment, an overall involution of the mass was documented (B).



**Figure 5.** Patients’ main clinical and radiologic findings which led to the diagnosis of giant cystic lymphangioma. Main steps in the management and follow-up are also reported.

### 3. Discussion

Most of the lymphangiomas are typically present at birth and are often diagnosed prenatally. In general, 80% of these malformations are diagnosed before the age of 2 years.<sup>[12]</sup> The cervicofacial region is most affected (approximately 50–75%).<sup>[13]</sup> They can also be found in the trunk, axilla, and extremities (42%). The mediastinal and abdominal locations are rare (10%).<sup>[2,14]</sup> Due to their permeative growth throughout all tissue layers, treatment is often challenging. The goal of LM management and treatment is to maintain functionality, control associated symptoms, and preserve aesthetic integrity.<sup>[2]</sup> In all cases, the treatment decision should be individualized and based on several factors, such as the type of malformation, size, location, growing trend, and associated symptoms.<sup>[1]</sup>

Surgical excision has been historically considered the treatment of choice for macrocystic and unicameral LMs, but resection is often incomplete with several complications (in particular bleeding, iatrogenic damages, and deformity) and high recurrence rate.<sup>[15]</sup>

Today less invasive therapeutic options are preferred. Small asymptomatic lesions can be carefully monitored since the possibility of spontaneous regression is described.<sup>[2,16–25]</sup> In other cases, sclerotherapy, laser therapy, and pharmacological treatment can be considered.<sup>[18,19]</sup>

Sildenafil, sirolimus, and propranolol are 3 oral medications that have been reported to be effective in the recent literature in the treatment of vascular anomalies.<sup>[3,21]</sup>

In particular, sirolimus has been demonstrated to be an efficacious and safe treatment for patients with complicated vascular anomalies, included cystic lymphangiomas and diffuse lymphangiomatosis that were refractory to other therapies.<sup>[3,22,23]</sup>

In our case series, patients were affected by giant cystic lymphangioma with multiple organ involvements (case 3). Surgical resection was performed primarily to relieve the airway obstruction and to prevent further complications, such as intracystic bleeding, cysts infection, nutritional problems (secondary to macroglossia and pharynx involvement). Given the infiltrative growth of these malformations, in all patients surgical excision was incomplete, and the risk of recurrence was high. Since the natural course of the disease could determine the progressive enlargement of residual cysts resulting in compression of the adjacent structures, organ dysfunction or erosion of the involved bones, a clinical, laboratory, and radiological follow-up was mandatory. As we expected, the lesion continued to grow after resection. Given the diffuse localization of the cystic elements and the involvement of vital structures, surgery was not applicable anymore. Sclerosing agents could not be injected because of the surrounding vessels and because cysts were numerous. Laser therapy was performed in one case to treat superficial localization in 1 patient (case 2). Therefore, in our patients, the most suitable therapy was a systemic pharmacological treatment. As reported in the recent literature, sirolimus has been demonstrated to be effective in the treatment of vascular anomalies, in particular in LMs and diffuse lymphangiomatosis.<sup>[3,22–25]</sup>

In all patients, after starting sirolimus therapy, a remarkable reduction in the size mass was demonstrated not only by the physical examination but especially in the radiological investigation. There was an overall decrease in mass extension, a reduction in cysts diameter and a global involution from macro- to the microcystic composition. In one case (patient 4), the first attempt

**Table 2****Blood analysis before and during sirolimus treatment.**

Time before/after	Case 1		Case 2		Case 3		Case 4	
	1 d	6 mo	1 d	5 mo	1 d	6 mo	2 mo	2.5 mo
Complete blood count								
White blood cells, 10 <sup>3</sup> /mmc	8.73	15.25	18.56	11.87	16.33	10	13.66	7.07
Red blood cells, 10 <sup>6</sup> /mmc	3.21	4.95	4.78	5.23	4.51	5.18	3.64	5.23
Hemoglobin, g/dL	9.4	12	10.6	9.6	11.5	12.2	13.9	13.2
Hematocrit, %	28.1	35	33.3	31.4	33.2	35.3	40.9	39.9
Platelet, 10 <sup>3</sup> /mmc	503	522	257	483	199	243	325	630
Biochemistry								
C reactive protein, mg/dL	0.25	0.38	0.33	0.04	0.07	0.03	0.03	0.02
Azotemia, mg/dL	12	21	33	25	31	26	31	17
Creatinine, mg/dL	0.14	0.25	0.21	0.21	0.51	0.44	0.8	0.24
Sodium, mEq/L	139	137	139	138	141	140	146	140
Potassium, mEq/L	5.1	6.2	4.8	5.3	5	3.5	3.7	5.1
Chloride, mEq/L	100	101	100	100	105	102	108	101
Calcium, mg/dL	10.31	10.34	10.07	9.87	10.27	10.43	9.36	10.75
Phosphate, mg/dL	6.6	5.2	5.1	5	6.1	4.9	5.2	6.2
AST, U/L	21	36	40	43	35	38	32	20
ALT, U/L	12	21	22	26	17	23	5	14
Alkaline phosphatase, U/L	265	195	252	187	287	276	161	275
Albumin, g/dL	3.7	4.5	4.5	4.1	4.6	4.9	3.3	3.7
Total cholesterol, mg/dL	119	226*	125	166	132	207*	126	173
LDL-C, mg/dL	67	166*	72.6	105	52	143*	87	109*
HDL-C, mg/dL	39	38	42	42	32	44	33	61
Triglycerides, mg/dL	86	108	52	92	84	178*	58	103

ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol.

\* Altered values.

with sirolimus was tried before surgical reduction of the mass size, and no clinical improvement was demonstrated. The failure of the initial treatment could be explained considering the broad distribution of the cysts and the difficulties we had in reaching and maintaining the desirable sirolimus blood levels. Indeed, the treatment was suspended for several times, making sirolimus ineffective. However, after surgical intervention, sirolimus was restarted, and blood levels were sufficiently stable. A progressive improvement was then observed.

Sirolimus was also effective in the treatment of diffuse lymphangiomatosis (case 3), as already reported in the recent literature.<sup>[24]</sup>

In the light of these considerations, we believe that sirolimus treatment is effective in case of small cysts and when stable blood levels can be maintained. In all other cases, a primary surgical reduction of the mass size should be taken into consideration in order to minimize the risk of ineffective pharmacological treatment.

In our experience, sirolimus was practically and efficiently managed by the patients' mothers. Compliance was good, thanks to the comfortable therapeutic scheme (oral administration 2 times/day). Sirolimus levels should be tested once a week in the first days of treatment. Once stable levels have been obtained, blood levels could be tested every 2 weeks and then monthly. Blood analysis should be performed monthly and should include a complete blood count, azotemia, creatinine, electrolytes, uric acid, albumin, total proteins, transaminase, total and fractioned bilirubin, total cholesterol, LDL and HDL cholesterol, triglycerides, C-reactive protein, immunoglobulins, lymphocytes populations, and protein electrophoresis. Urine culture should also be obtained. Blood analysis and cultures should be performed at any time patient shows clinical signs of infection or has new symptoms which could be related to sirolimus

treatment. As concerns radiological follow-up, we suggest to perform a serial ultrasound, with a frequency depending on radiological findings, and an MRI scan with contrast after 3 to 6 months therapy have been started. The main and isolated adverse effect we observed at laboratory analysis was progressive dyslipidemia, with increasing levels of total cholesterol (in particular LDL fractions) and triglycerides in 3 out of 4 patients. No other complications secondary to sirolimus administration were observed (Table 2).

#### 4. Conclusions

Sirolimus is a safe and effective therapy in the management of multicystic and diffuse LMs. In particular, we recommend the use of sirolimus after unsuccessful surgical excision have been tried or when the surgical approach is not feasible, for example when multiple localizations or diffuse lymphangiomatosis are present. We suggest the therapeutic scheme of 0.4 to 0.8 mg/m<sup>2</sup> 2 times/day. The dosage should be adjusted to maintain sirolimus blood levels between 10 and 15 ng/mL. A multidisciplinary follow-up should be started.

To date, our experience with sirolimus in the management of LMs is favorable and poor disadvantages have been observed. However, in our clinical records follow-up is limited and a longer time is needed to monitor potential complications and disease evolution.

We wish for the use of sirolimus for the treatment of LMs could be better characterized in the setting of a formal clinical trial.

#### 4.1. Informed Consent

The patient's parents provided their written informed consent for the publication of this case report.

## Acknowledgments

The authors would like to thank all nurses and neonatologists of the NICU, surgeons of the Department of Pediatric Surgery, surgeons of the Department of Otolaryngology, pediatric radiologists of the Pediatric Radiology Unit, anesthesiologists of the Pediatric Anesthesiology and Intensive Care Unit, nurses of the operating room of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico.

## References

- [1] Ernemann U, Kramer U, Miller S, et al. Current concepts in the classification, diagnosis and treatment of vascular anomalies. *Eur J Radiol* 2010;75:2–11.
- [2] Amodeo I, Cavallaro G, Raffaelli G, et al. Abdominal cystic lymphangioma in a term newborn: a case report and update of new treatments. *Medicine* 2017;96:e5984.
- [3] Adams DM, Trenor CC, Hammil AM, et al. Efficacy and safety of Sirolimus in the treatment of complicated vascular anomalies. *Pediatrics* 2016;37:e20153257.
- [4] Hammil AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* 2011;57:1018–24.
- [5] Lee DF, Hung MC. All roads lead to mTOR: integrating inflammation and tumor angiogenesis. *Cell Cycle* 2007;6:3011–4.
- [6] Kobayashi S, Kishimoto T, Kamata S, et al. Rapamycin, a specific inhibitor of the mammalian target of rapamycin, suppresses lymphangiogenesis and lymphatic metastasis. *Cancer Sci* 2007;98:726–33.
- [7] Neuhaus P, Klupp J, Langrehr JM. mTOR inhibitors: an overview. *Liver Transpl* 2001;7:473–84.
- [8] Huber S, Bruns CJ, Schmid G, et al. Inhibition of the mammalian target of rapamycin impedes lymphangiogenesis. *Kidney Int* 2007;71:771–7.
- [9] Masabumi S. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis. A crucial target for anti- and pro-angiogenic therapies. *Genes Cancer* 2011;2:1097–105.
- [10] Klumpen HJ, Beijnen JH, Gurney H, et al. Inhibitors of mTOR. *Oncologist* 2010;15:1262–9.
- [11] Ji Y, Chen S, Xiang B, et al. Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: a multicenter retrospective study. *Int J Cancer* 2017;141:848–55.
- [12] Bailey CM. Cystic hygroma. *Lancet* 1990;335:511–2.
- [13] Brennan TD, Miller AS, Chen SY. Lymphangiomas of the oral cavity: a clinicopathologic, immunohistochemical and electron-microscopic study. *J Oral Maxillofac Surg* 1997;55:932–5.
- [14] Cahill AM, Nijis EL. Pediatric vascular malformations: pathophysiology, diagnosis, and the role of interventional radiology. *Cardiovasc Intervent Radiol* 2011;34:691–704.
- [15] Edwards PD, Rahbar R, Ferraro NF, et al. Lymphatic malformation of the lingual base and oral floor. *Plast Reconstr Surg* 2005;115:1906–15.
- [16] Greene AK, Perlyn CA, Alomari AI. Management of lymphatic malformations. *Clin Plast Surg* 2011;38:75–82.
- [17] Perkins JA, Manning SC, Tempero RM, et al. Lymphatic malformations: review of current treatment. *Otolaryngol Head Neck Surg* 2010;142:795–803.
- [18] Churchill P, Otal D, Pemberton J, et al. Sclerotherapy for lymphatic malformations in children: a scoping review. *J Pediatr Surg* 2011;46:912–22.
- [19] Railan D, Parlette EC, Uebelhoefer NS, et al. Laser treatment of vascular lesions. *Clin Dermatol* 2006;24:8–15.
- [20] Swetman GL, Berk DR, Vasanawala SS, et al. Sildenafil for severe lymphatic malformations. *N Engl J Med* 2012;366:384–6.
- [21] Ozeki M, Kanda K, Kawamoto N, et al. Propranolol as an alternative treatment option for pediatric lymphatic malformation. *Tohoku J Exp Med* 2013;229:61–6.
- [22] Margolin JF, Mills Soni H, Pimpalwar S. Medical therapy for pediatric vascular anomalies. *Semin Plast Surg* 2014;28:79–86.
- [23] Akyuz C, Atas E, Varan A. Treatment of a tongue lymphangioma with sirolimus after failure of surgical resection and propranolol. *Pediatr Blood Cancer* 2014;61:931–2.
- [24] Laforgia N, Schettini F, De Mattia D, et al. Lymphatic malformation in newborns as the first sign of diffuse lymphangiomatosis: successful treatment with sirolimus. *Neonatology* 2016;109:52–5.
- [25] Kim D, Benjamin L, Wysong A, et al. Treatment of complex periorbital venolymphatic malformation in a neonate with a combination therapy of sirolimus and prednisolone. *Dermatol Ther (Heidelb)* 2015;28:218–21.