CASE REPORT

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Rapid response with good toleration of sirolimus for life-threatening neonatal lymphatic malformations

Shixiao Dong[1]* | Li Li[2]* | Jiaosheng Xu[3] | Zhonglong Han[4] | Xia Zheng[1]

[1]Department of Neonatology, Neonatal Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Department of Dermatology, Plastic Surgery Hospital, Chinese Academy of Medical Sciences, Beijing, China
[3]Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[4]Department of Radiology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Jiaosheng Xu, Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China.
Email: xujiaosheng@sina.com

*These authors contributed equally to this work.

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ABSTRACT

Introduction: Lymphatic malformations (LMs) are rare vascular anomalies predominantly affecting infants, which can be debilitating or life-threatening when complicated with intralesional bleeding or infection. Effective and safe management strategies are essential in such cases.

Case presentation: We report a case series involving four Chinese neonates with life-threatening LMs, initially treated with oral sirolimus. All patients achieved rapid relief and sustained remission, using a lower sirolimus dosage than previously recommended. Furthermore, adverse events were rarely recorded during follow-up.

Conclusion: Sirolimus can be considered a promising choice for neonates with intricate and life-threatening LMs. Initiation with a reduced sirolimus dose is advisable.

KEYWORDS

Dosage, Lymphatic malformations, Neonates, Sirolimus

INTRODUCTION

Lymphatic malformations (LMs) are rare congenital vascular anomalies characterized by the accumulation of abnormal lymph fluid. Approximately half of LMs are detected at birth, and most occur in the head and neck region.[1] The manifestation of LMs can be diverse, ranging from regional swelling to extensive diffusely infiltrating masses that may compromise adjacent structures. LMs occurring in the head and neck region may present with airway obstructions, feeding problems, and deformities. Moreover, LMs can be debilitating and life-threatening when complicated with intralesional bleeding or infection, which is frequently observed in neonatal LMs.[2] Historically, surgical resection and sclerotherapy have been considered as the management procedures for LM.[3] Indeed, pharmaceutical treatment is highly desirable for neonatal patients with life-threatening and complicated LMs. The successful use of sirolimus has been reported in neonates with LMs after surgical resection and/or

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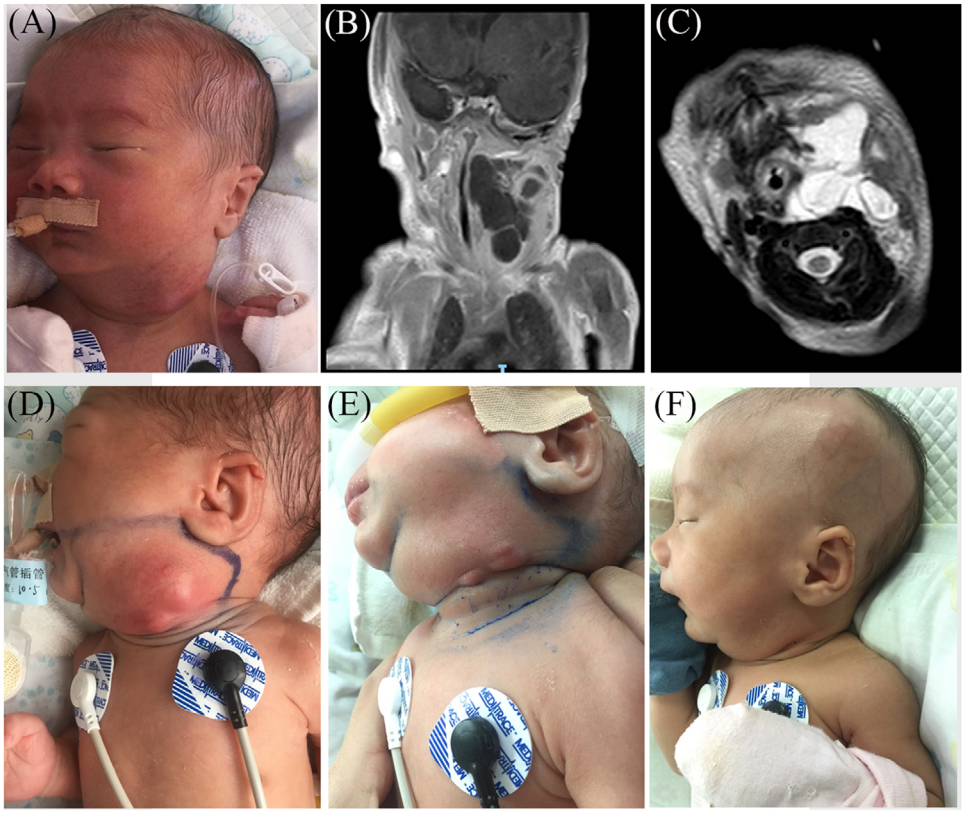

FIGURE 1 The images of patient 1 with lymphatic malformations (LMs). (A) LMs on the left aspect of the neck on the fourth day of life (DOL). (B) Coronal gadolinium-enhanced T1-weighted and (C) axial T2-weighted magnetic resonance imaging showed multiple macro-cysts with trachea depression. (D) Rapid mass growth led to progressive tachypnea on DOL 13. (E) The mass started to shrink on DOL 18 after sirolimus treatment. (F) A remarkable reduction of the mass was observed on DOL 30.

sclerotherapy failure.[4,5] Here, we report the cases of four Chinese neonates with life-threatening LMs initially treated with oral sirolimus.

CASE REPORT

Patient 1

A 33^{+4}-week preterm male neonate, with unremarkable prenatal history, was transferred to our hospital on the fourth day of life (DOL) with a progressively enlarged subcutaneous mass. On the day before admission, an elevated and soft mass measuring 3 cm × 3 cm was noted over the left aspect of the neck without warmth or pain. On admission, the mass enlarged to 5 cm × 4.5 cm in size, redness was noted, and the mass was firm (Figure 1A). Routine blood tests showed a C-reactive protein (CRP) level of 14 mg/L, white blood cell (WBC) count of 1.72 × 10^9/L, neutrophil count of 52.9%, and normal count of red blood cells and platelets. Ultrasonography revealed multiple cystic anechoic areas, indicating a diagnosis of LMs. Repeated blood tests revealed an increased CRP (45 mg/L) and decreased WBC count (1.5 × 10^9/L). Biochemistry showed a decrease in albumin level (26.3 g/L; reference: 35–55 g/L) and normal liver and kidney function. His coagulation profile revealed a distinct prolonging activated partial thromboplastin time of 84.2 s (reference: 25.1–38.4 s). Severe systemic infection was suspected. On DOL 5, the patient received meropenem (20 mg/kg) every 12 h and his blood was cultured repeatedly. Central nervous system infection was ruled out as the cerebrospinal fluid test was normal. Simultaneously, he developed paroxysmal tachypnea and was alleviated by nasal continuous positive airway pressure (NCPAP)-assisted ventilation. On DOL 11, WBC and CRP levels normalized and NCPAP was discounted without dyspnea. On DOL 12, the patient was breathing independently and fed well. Meropenem was discontinued. The blood culture was positive for *Escherichia coli*, which was sensitive to meropenem. The magnetic resonance imaging showed multiple left cervical macro-cysts, extending from the sphenoid bone to thoracic inlet. These cysts were found to emcompress the branch of the aorta, as well as cause obstruction in the airway, resulting in a shift towards the right (Figure 1B, C). The lesions were widespread and extensive, making them unsuitable for surgical resection or sclerotherapy. On DOL 13, the patient developed progressive tachypnea due to rapid growth of

the mass, with presumed intralesional bleeding without relief after NCPAP support (Figure 1D). Immediate intubation was initiated, and medication to control the LMs was considered. After obtaining written consent from the parents, oral sirolimus was started at a dose of 0.1 mg/d (0.6 mg/m^2) on DOL 16. Surprisingly, the mass started to shrink, and the patient was extubated on DOL 18 (Figure 1E). The blood concentration of sirolimus was measured at 5.96 ng/mL on the second day of administration and 19.67 ng/mL and 19.97 ng/mL on the sixth and eighth days, respectively. The dosage of sirolimus was adjusted to 0.0625 mg/d (0.38 mg/m^2) and the level returned to the target range (9.85–12.35 ng/mL). The boy responded well to therapy, and the mass had almost disappeared on inspection on DOL 30 (Figure 1F). Oral feeding was restarted on DOL 28, and the boy was discharged home on DOL 32. At the follow-up visit on DOL 60, the boy was found to be growing well. Sirolimus therapy was continued without recurrence. The patient was still under close long-term follow-up.

Patients 2–4

The other three neonates visited our hospital with giant head and neck masses and subsequent dyspnea and/or dysphagia. All patients were diagnosed with complicated LMs based on clinical and radiologic findings. The complications improved via intubation and/or tube feeding. After obtaining informed consent from the parents of all children, the primary use of oral sirolimus therapy was started to reduce the masses. All patients achieved prompt remission and were discharged home with natural breathing and spontaneous milk intake. No side effects were reported. Clinical data, treatment details, serum sirolimus concentrations (Figure S1), and adverse events were recorded in Table 1 and Figures S2 and S3.

DISCUSSION

Neonatal patients who suffer from complicated LMs in the head and neck are difficult to treat. First, timely ventilation and feeding support are required immediately when respiratory distress and dysphagia occur, as shown in our study. Tracheostomy is proposed when the indication of tracheostomy has been established in complicated LMs.[2] Our data show that the optimal ventilatory support is noninvasive ventilation, such as NCPAP, while intubation in some cases is unavoidable. Tracheostomy is suggested to be avoided as much as possible. Second, rapidly effective treatments targeting mass reduction are urgent after complications (particularly dyspnea and infection) are managed. Long-term ventilation and feeding support may result in secondary infection, nutrition problems, and impaired speech development. Concurrently, the mass will continue to grow and may exacerbate the process. Third, the side effects underlying each therapy should be considered. In particular, indirect damage to the vital structures in the head and neck needs to be prevented. Furthermore, recurrence and aesthetic impairment also need to be evaluated.

To date, there are no guidelines for managing complicated LMs in neonates. Surgery and sclerotherapy are effective for macrocystic LMs, while microcystic or mixed LMs remain challenging due to their infiltrative nature. Furthermore, it is usually impossible to perform complete surgical resection of extensive LMs, and resection is often associated with several complications, including bleeding, iatrogenic damage, deformity, and a high recurrence rate for giant and complicated LMs. Sclerotherapy requires a high-quality experienced operator for deep lesions and complicated structures in critically ill neonates. In addition, surgery and sclerotherapy require long hospital and intensive care unit stays for recovery.[3] Sildenafil, sirolimus, and propranolol are three oral medications that have been reported to be effective in the treatment of vascular anomalies.[1] Although severe lymphatic malformation was successfully treated with sildenafil, the overall effective rate of oral sildenafil was unremarkable. Propranolol is a potential alternative for LMs. However, propranolol may control bleeding instead of reducing tumor volume in patients with LMs.

As activation of the PIK3CA/Akt/mTOR signaling pathway is widely detected in LMs, several therapies targeting this pathway have emerged. Sirolimus was the first targeted regime successfully used in LMs. Sirolimus is an mTOR inhibitor that inhibits the pathway downstream of PIK3CA/Akt/mTOR and activates protein synthesis, resulting in cell proliferation and increased angiogenesis, thus playing a key role in the pathogenesis of various vascular anomalies, including LMs.[6] Over the last decade, the successful use of sirolimus has been increasingly reported in children with LMs and kaposiform hemangioendotheliomas.[7] Alpelisib, a PIK3CA inhibitor that can directly target PIK3CA/Akt/mTOR signaling pathway, was also effectively used in LM.[8] Another activated pathway involved in LMs is the RAF/ERK/MEK signal pathway.[9] Trametinib, a MEK inhibitor acting on this pathway, was also successfully administered in treating LMs.[10]

As LMs are extensive or combined with intralesional bleeding and/or infection in our series, we used oral sirolimus instead of surgery and sclerotherapy. All patients received short-term noninvasive ventilatory support and/or gastric tube feeding. After concomitant infection improved, a sirolimus dose targeting a trough level of 10–15 ng/mL was administered orally. The LMs shrunk or softened promptly. The mean time to effect was 4.5 days (range, 2–8 days), which was shorter than surgery and sclerotherapy.[3]

TABLE 1 Characteristics of the neonates with life-threatening lymphatic malformations.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
History				
Prenatal diagnosis	None	Mandibular cyst	None	None
Gestational age (week)	33^{+4}	39^{+3}	40	41
Delivery mode	CS	CS	CS	Vaginal delivery
Sex	Male	Female	Male	Male
Birth weight (g)	1950	3100	4400	3690
Apgar score (1'/5')	10/10	NA	NA	NA
Days of intubation before medication	3	3	0	6
Days of NCPAP before medication	6	0	0	0
Days of GT before medication	0	0	13	7
Clinical findings				
Physical examination	Left cervical mass, reddish discoloration of the skin	Anterior cervical mass, normal skin; macroglossia	Extensive mass from the right preauricular area to the neck, normal skin	Left cervical mass, normal skin; macroglossia
Radiography findings	US and CT: macrocystic	US and MRI: mixed cystic	US and CT: mixed cystic	US and MRI: mixed cystic
Localization	Parapharyngeal space, retropharyngeal wall, aorta, and trachea	Cervical muscles, tongue basis, trachea, larynx, submandibular, parotid gland, and salivary gland	Retropharyngeal wall, tongue basis, parapharyngeal space, parotid gland, submandibular gland, and cervical muscles	Submandibular, parotid, and salivary glands, aorta, retropharyngeal, parapharyngeal space, and upper mediastinum
Maximum diameter of the cysts (cm)	4.5	2.9	4.1	2.7
Complications	Intracystic bleeding, infection, and airway obstruction	Airway obstruction, macroglossia, and dysphagia	Macroglossia, dysphagia, intralesional bleeding, and infection	Macroglossia, dysphagia, and infection
Sirolimus therapy				
DOL of initiation	16	19	36	26
Dosage of initiation ($mg \cdot m^{-2} \cdot d^{-1}$)	0.60	1.16	1.00	0.49
Dosage adjusted ($mg \cdot m^{-2} \cdot d^{-1}$)	0.38	0.48	0.50	0.58
Clinical outcomes	Reduction of mass size	Reduction of mass size	Soften in texture and reduction of mass size	Reduction of mass size
Days of intubation after medication	2	7	0	0
Days of NCPAP after medication	8	0	0	8
Days of GT after medication	0	0	9	12
Radiography findings	Reduction of mass size	Reduction of mass size	Stabilization of the mass	NA

(Continues)

TABLE 1 (Continued)

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Other treatment				
Antibiotics	Meropenem	Ceftazidime	Ceftazidime	Ceftazidime
Adverse effects	No	No	No	No
Follow-up				
Treatment duration (month)	5	13	6	6, lost to follow-up
Ongoing treatment	Yes	Yes	No	NA
Other therapies	No	No	Sclerotherapy	NA

Abbreviations: CS, cesarean section; CT, computed tomography; DOL, day of life; GT, gastric tube; MRI, magnetic resonance image; NA, not available; NCPAP, nasal continuous positive airway pressure; US, ultrasound.

Intubation and tube feeding could also be discontinued over time. The median time of intubation or oral gastric tube feeding after sirolimus was 9.5 days (range, 7–12 days). All patients were discharged in room air and had spontaneous milk intake. Our patients demonstrated positive responses to therapy, which is similar to recent reports in neonates with LMs.[11] During the hospitalization and follow-up period, no adverse events were recorded in the patients. However, it is essential to remain cautious about the potential adverse events associated with sirolimus therapy. Long-term follow-up is needed, particularly in infant patients. The most common side effect of sirolimus is the toxicity of blood and bone marrow. Other adverse effects reported included hyperlipidemia, hypertension, and renal dysfunction. Due to the potential immunosuppression of sirolimus, there is a high risk for infections. And reports have shown serious adverse events including death due to fatal infections in very young infants treated with oral sirolimus.[12]

Another debated topic is the proper dose of sirolimus for neonatal patients. The initially suggested dosage of sirolimus is $1.6\,mg{\cdot}m^{-2}{\cdot}d^{-1}$ and the pharmacokinetic-guided target serum trough levels range from 10 to 15 ng/mL. Patient 2 received a relatively higher dose than other patients but was within the suggested range ($1.16\,mg{\cdot}m^{-2}{\cdot}d^{-1}$); subsequently, the blood level exceeded the trough level during the following concentration measurement. Other patients started at a lower dosage (range: $0.49–1\,mg{\cdot}m^{-2}{\cdot}d^{-1}$). Two of them exceeded the target concentration, and the dosage was adjusted (0.38. and $0.5\,mg{\cdot}m^{-2}{\cdot}d^{-1}$). The initial dosages required to attain the target concentration in our patients were lower than those previously reported. Even a very low initial dose of sirolimus ($0.49\,mg{\cdot}m^{-2}{\cdot}d^{-1}$), which resulted in a sirolimus blood concentration of 3.28–4.15 ng/mL, was effective for mass reduction in Patient 4. This phenomenon was also observed in very young infants with vascular anomalies when treated with sirolimus.[13,14] The pharmacokinetic analysis showed a lower sirolimus clearance in neonates than in elderly children.[15] It is essential to realize that during the first months of life, metabolism is still developing and enzymes necessary to metabolise drugs like sirolimus still have to mature. Thus, these studies suggest that a lower dose of sirolimus may offer the same therapeutic benefit while minimizing adverse effects. Therefore, we propose a lower initial dose for neonates who receive oral sirolimus therapy. However, the precise initial dosage should be individualized and the sirolimus dosage should be based on age and the associated pharmacological developments.

In conclusion, sirolimus shows favorable response and tolerance in neonatal head and neck LMs. It may be a suitable option for neonatal patients with complicated and life-threatening LMs, with a lower initial dosage. Large studies are necessary to confirm the role of sirolimus in neonatal LM treatment.

CONSENT FOR PUBLICATION

The patients' parents have given informed consent.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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