doi: 10.67071/3093-9038-2026-25-06-34-40

TREATMENT OF CYSTIC LYMPHATIC MALFORMATIONS IN NEWBORNS AND INFANTS

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Introduction. Cystic lymphatic malformations are genetically determined malformations of the lymphatic vessels. In approximately 50-75% of cases, clinical manifestations are present by birth. Large lesions in newborns and infants can cause life-threatening complications due to compression of internal organs.

Materials and methods. Between 2017 and 2024, 10 patients with abdominal CLM were treated in the neonatal and infant surgery department of the National Medical Research Center for Children's Health of the Russian Ministry of Health. The patients ranged in age from 25 to 158 days (seven girls and three boys). All patients underwent radical removal of the tumor via laparotomy; some also underwent small bowel resection. Intraoperative specimens were sent for histological and molecular genetic testing.

Results. Radical removal of cystic lymphatic malformations was performed in all children (n=10); in cases of tumor invasion into the small intestinal wall (n=3), resection (10–12 cm) with interintestinal anastomosis was performed. Restoration of intestinal passage occurred within 2 to 5 days. In the presence of an intact intestinal wall, resection was not performed; restoration of intestinal passage occurred on the 2-4th postoperative day, on average on the 3rd postoperative day. Postoperative complications in the form of lymphorrhea (n=4) were stopped by the appointment of conservative therapy with octreotide. Based on the results of molecular genetic testing, the PIK3CA mutation (n=9) and CLOVES syndrome (n=2) were detected; targeted therapy with a phosphatidylinositol-3-kinase inhibitor was prescribed with a pronounced positive effect.

Conclusion. In the neonatal period, cystic lymphatic malformations can cause complications, necessitating urgent surgical treatment. Conservative therapy should only be prescribed if there is no risk of life-threatening complications.

Molecular genetic testing is essential for all patients with cystic lymphatic malformations to detect overgrowth syndrome disorders as early as possible and initiate targeted therapy. These patients should be referred to a pediatric oncologist to determine the need for targeted therapy. Periodic follow-up is essential, as the clinical manifestations of overgrowth syndromes may not be obvious at birth, and the presence of a lymphatic malformation may be only the first manifestation of a syndromic pathology.

Key words: *cystic lymphatic malformations, neonates, octreotide*.

Introduction. Cystic lymphatic malformations are genetically determined malformations of the lymphatic vessels. According to the classification of the International Society for the Study of Lymphatic Malformations (ISSVA), cystic lymphatic malformations are classified as slow-flow malformations.

Lesions greater than 2 cm in diameter are considered macrocystic, while those less than 2 cm are considered microcystic [1,2]. One of the possible causes of the development of a particular type of cystic malformation is the structure of the surrounding connective tissue. The presence of a more compact stroma leads to the formation of microcystic lesions, while loose connective tissue allows for the development of large cystic lesions.

Overall, lymphatic malformations account for approximately 10% of all vascular anomalies. Lymphatic malformations develop beginning in the second month of fetal development, when the primary lymphatic system emerges [3]. In approximately 50-75% of cases, clinical manifestations of a lymphatic anomaly are present by birth. Large lesions can lead to the development of severe infectious complications, cause dysphagia, and respiratory distress due to compression of adjacent organs. Their superficial location can result in significant cosmetic defects that significantly reduce quality of life [2, 4, 5, 6]. Even within a single nosological entity, the clinical manifestations of lymphatic malformations vary widely, ranging from asymptomatic progression to severe life-threatening conditions.

Cystic lymphatic malformations are most often located in the areas of formation of embryonic lymphatic sacs, which give rise to the primary lymphatic plexus [2, 7].

The vast majority of lymphatic malformations are localized in the neck (about 75%) and axillary region (20%), much less often they spread into the mediastinum, the most rare are malformations originating from the ilioinguinal primary lymphatic sac [6, 8, 9, 10, 11].

Structurally, cystic lymphatic malformations are represented by thin-walled, cystically dilated lymphatic vessels (Figure 3a) with an irregular, wide lumen, lined by flat endothelial cells with scanty cytoplasm compared to the endothelial cells of blood vessels [12, 13]. In the walls of the formation, bundles of abnormally oriented smooth muscle cells, clusters of lymphocytes, and plasmacytoid dendritic cells (a population of immune cells that play an important role in the interaction of innate and acquired immune responses) are found.

Such accumulations of lymphocytes and plasmacytoid dendritic cells are observed in various inflammatory, autoimmune, infectious and neoplastic processes in the body and are called tertiary lymphoid organs (Figure 3b). Their formation is possibly associated with low lymph flow within the lymphatic malformation, which contributes to the retention of immune cells, which in turn can contribute to the growth of the formation by producing lymphotoxin and other lymphangiogenic factors. Plasmacytoid dendritic cells are a population of immune cells specializing in the production of interferon [14]. Fibrosis and signs of inflammatory infiltration are often detected in the stroma. Macrocystic and microcystic lesions of any localization are indistinguishable by histological and immunohistochemical examination, but the nature of the formation may depend on the anatomical microenvironment [15]. Markers of the lymphatic phenotype of the endothelium are CD31+, podoplanin. Podoplanin is considered to be the most reliable marker for lymphatic vessels [12, 13, 16, 17].

The mechanism underlying the formation of each type of cystic lymphatic malformation remains unclear. However, recent progress has been made in understanding this issue: differences in gene

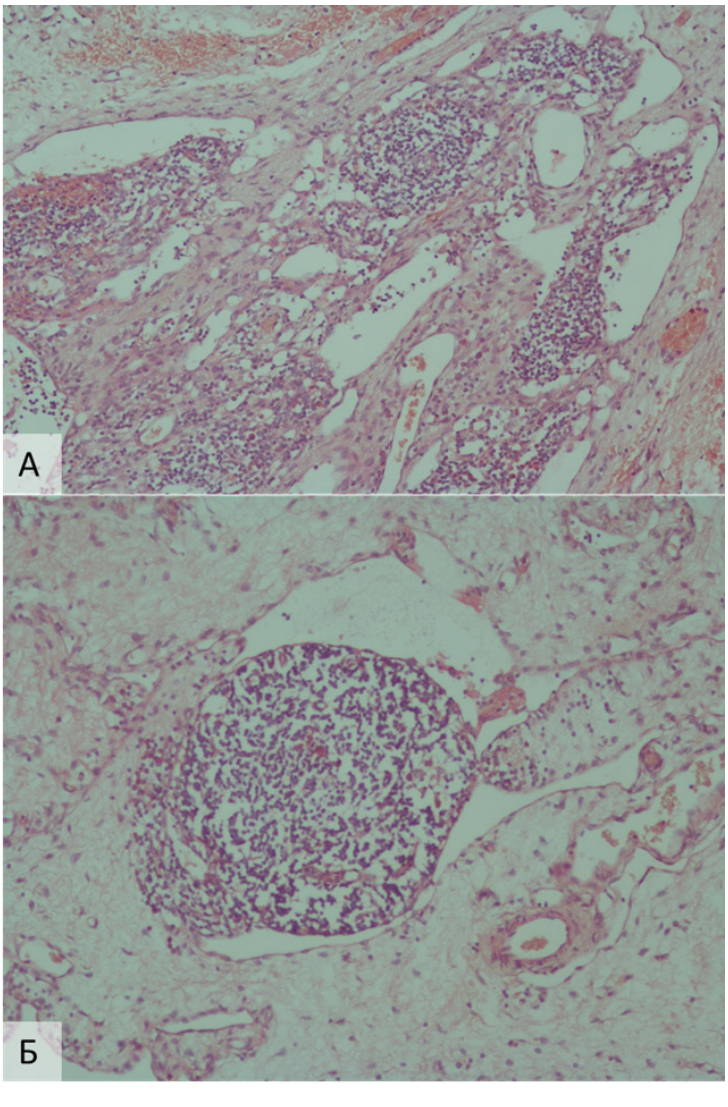

Figure 1. Lymphocytic clusters of follicular type (hematoxylin and eosin, x)

expression have been identified between macro- and microcystic malformations despite identical histological and immunohistochemical findings. Microcystic malformations exhibit hyperactivation of anti-apoptotic and proliferative mechanisms, as well as overexpression of matrix metalloproteinase-9, which leads to dissolution of the extracellular matrix, the release of proangiogenic factors, and stimulation of endothelial cell migration and invasion. This may explain the difficulty of radical removal and the high recurrence rate of the microcystic component after surgery. Macrocystic malformations have been shown to exhibit disturbances in the regulation of cellular respiration and adaptation to hypoxia. Matrix remodeling, migration and development of the endothelium under hypoxic conditions leads to the formation of wide lumens observed in this form of malformation [18].

Lymph endothelial cells develop from venous precursors via a "centrifugal" pathway and from paraxial mesoderm cells via a "centripetal" pathway under the influence of a number of growth factors that influence the migration and polarization of endothelial cells [3, 7, 19, 20, 21]. In this case, the intracellular PI3K-AKT-mTOR pathway is used as the main signal transduction pathway. In 80% of cystic lymphatic malformations, the causative mutation was identified in the gene encoding phosphatidylinositol-3-kinase. This mutation leads to excessive growth due to the activation of the PI3K-AKT-mTOR pathway [22]. Thus, this provides a theoretical basis for the possibility of obtaining a positive effect from the use of PI3K and mTOR inhibitors. In 2014, a group of rare diseases caused by a somatic mutation in PIK3CA—the PIK3CA-Related Overgrowth Spectrum (PROS)–was identified. One of the clinical manifestations of this pathology is the presence of vascular anomalies with reduced blood flow, including lymphatic ones. Currently, the question of whether isolated lymphatic malformations should be considered part of the spectrum of overgrowth syndromes with minimal manifestations or classified as related disorders outside the spectrum of overgrowth syndromes remains controversial [2, 23, 24].

Purpose of the study. Improving treatment outcomes in neonates and infants with abdominal cystic lymphatic malformations.

Materials and methods. Between 2017 and 2024, nine patients with cystic (macrocystic and microcystic) lymphatic malformations of the abdominal cavity were treated in the Surgical Department of Neonates and Infants at the National Medical Research Center for Children's Health of the Russian Ministry of Health. The patients' ages ranged from 25 to 158 days (six girls and three boys). All patients underwent a standard set of laboratory tests prior to surgery upon admission: a complete blood count, urinalysis, blood chemistry, coagulation profile, blood type, and Rh factor. Also, given the presence of a space-occupying lesion, tumor marker tests (alpha-fetoprotein, ferritin, lactate dehydrogenase, alkaline phosphatase, and neuron-specific enolase) were performed.

All patients underwent radical removal of the tumor via laparotomy; some also underwent small bowel resection (due to tumor extension). Intraoperative specimens were sent for histological and molecular genetic testing.

Results. Most patients were full-term and had good growth and weight indicators at birth. No intrauterine complications related to the presence of the lymph node mass were identified. Only one case required an emergency cesarean section at 30 weeks of gestation due to life-threatening paroxysmal tachycardia in the fetus, which manifested as compression by the mass. Seven patients

Table 1. Albumin levels in patients with cystic lymphatic malformations

The nature of the malformation	Body weight (g)	Size of formation (cm)	Volume of formation (cm3)	Albumin level (g/L)
large cystic	3050	9,6x7,6x7,3	282,3	29
	3560	10,0x6,0x7,0	420,0	30
	2990	10,9x4,6x8,3	220,6	31
	4110	6,9x7,2x11,6	305,4	23
microcystic	3300	2,5x2,7x8,3	56,0	33,4
	4980	3,5x3,0x4,7	49,4	37
mixed	3890	2,3x4,5x5,6	57,9	41,1
	4670	4,5x3,0x2,5	33,7	43,2
	6180	4,5x3,5x3,0	47,5	43,4

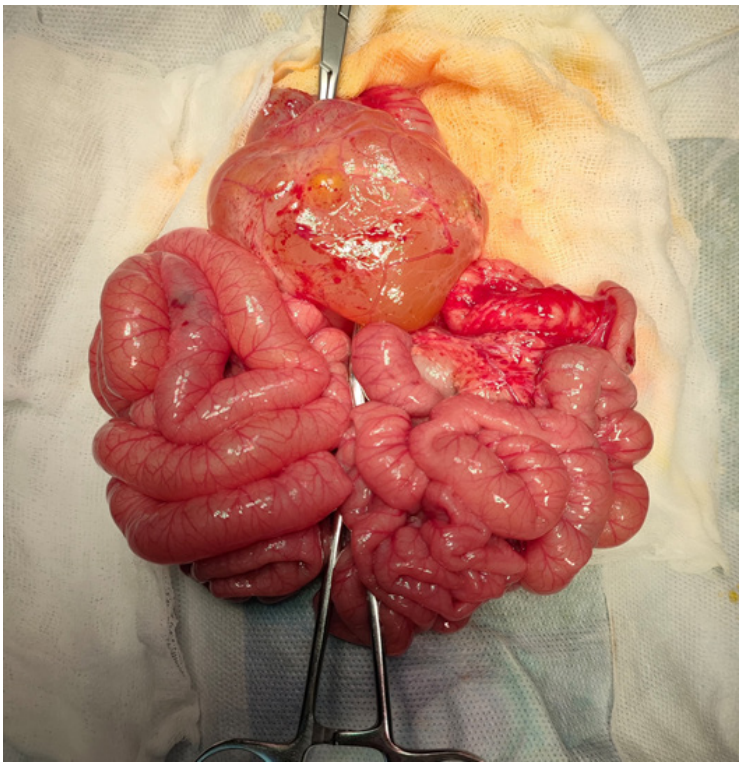

Figure 2. Lymphatic malformation of the abdominal cavity

developed complications in the preoperative period due to compression of vital organs by the lymph node mass, including respiratory failure, partial intestinal obstruction, and paroxysmal tachycardia.

Patients with large cystic lymphatic malformations were characterized by hypoalbuminemia associated with pathological losses in the cavity of the formation (see Table 2).

For radical removal of the cystic lymphatic malformation, all patients underwent laparotomy, abdominal exploration, and isolation of the lesion within healthy tissue. Figure 2 shows the intraoperative image of the lesion.

When the tumor invaded the intestinal wall, resection of the affected area was performed with the creation of an interintestinal anastomosis (n=3). The length of the removed section did not exceed 10–12 cm, which, given the normal overall intestinal length, did not affect digestive function. Restoration of intestinal passage occurred within 2 to 5 days. If the intestinal wall was intact, resection was not performed; intestinal passage was restored within 2–4 postoperative days, with an average of 3 postoperative days.

Postoperative complications, such as lymphorrhea, were observed in 4 cases and were managed with conservative therapy with octreotide. Octreotide was prescribed off-label based on the criteria of a life-threatening condition, the absence of registered pathogenetic therapy, and documented efficacy. The drug was administered intravenously through a separate venous access continuously at a dose of 10-12 mcg/kg/hour while maintaining total parenteral nutrition. Once lymphorrhea resolved, the drug was gradually discontinued and enteral feeding was resumed with a therapeutic mixture with a reduced content of long-chain fatty acids and an increased content of medium-chain triglycerides.

We conducted an analysis of the influence of the volume of the formation on the development of postoperative lymphorrhea (Table 4).

No statistically significant differences (p=0.439) (method used: Mann–Whitney U test) were obtained, which allowed us to conclude that the size of the formation does not affect the risk of developing lymphorrhea in the postoperative period.

All patients also underwent molecular genetic testing: the PIK3CA mutation was detected in 8 of 9 cases. Hotspot analysis showed that the most common mutation, E545K, is characteristic of cystic lymphatic malformations; it was detected in 6 cases (75%), while a mutation at hotspot E542K was noted in 2 cases (25%). In two cases, the diagnosis of CLOVES syndrome (Congenital Lipomatous

Table 4. Analysis of the influence of the volume of formation on the development of postoperative lymphorrhea

Categories	Volume of formation V			p
	Me	Q1 – Q3	n	
No complications	56,20	30,10 – 249,40	5	0,439
Lymphocytosis	220,60	170,15 – 251,45	4	

Overgrowth, Vascular Malformations, Epidermal Naevi, Scoliosis/Skeletal and Spinal Syndrome) was confirmed. These patients presented with a combination of congenital lipomatosis, lymphatic malformation, epidermal nevus, and skeletal developmental anomalies. In both cases, mutations were identified at the hotspots: E545R (n=1) and E542K (n=1). CLOVES syndrome is an extremely rare disorder with an incidence of less than 1 case per 1,000,000 people. The children were prescribed targeted therapy with a phosphatidyl-inositol 3-kinase inhibitor, which showed significant positive results.

Discussion. Antenatal ultrasound diagnosis of lymphatic malformations is often possible from the second trimester of pregnancy [25]. Given the large number of reports on the combination of lymphatic malformations with various syndromes (Shershevsky-Turner, Down, Klippel-Trenaunay-Weber, Gorham, Noonan, Recklinghausen, Edwards, Patau, CLOVES) [26], when they are detected, it is recommended to study the karyotype of the fetus, prenatal counseling of expectant parents in order to make a decision on prolonging the pregnancy, determining the method of delivery and further tactics.

Ultrasound is used to diagnose lymph nodes of various localizations. In the case of cysts, it is used to visualize an anechoic formation with a distinct external contour and septa without blood flow; only slight blood flow may be recorded in the septa. In the case of hemorrhage or the addition of an infection, the nature of the echo signal from the contents may change [10, 11]. In cases of complex anatomical localization, magnetic resonance or computed tomography is used to clarify the nature of the process. The study can use antiphase in-phase/out-of-phase (IP/OOP) sequences; a homogeneous decrease in the intensity of the MR signal on the OOP sequence of liquid contents indicates its chylous nature [8, 11].

Treatment of lymphatic malformations and postoperative lymphorrhea, depending on the type, location, and extent of the lesion, can be surgical, conservative, or a combination of both [1]. Expecting spontaneous regression is currently not considered justified, as studies have shown that even with reduction in the volume of the lesion, complete spontaneous regression is impossible. Given current views on the origin and existing classification of lymphatic malformations, surgical intervention is no longer an absolute priority or the only possible treatment option.

In the structure of surgical treatment methods, the leading role is undoubtedly played by the removal of a space-occupying lesion within healthy tissues [1]. Radical resection is possible in approximately 60% of cases of cystic lymphatic malformations, more often this concerns large cystic formations [21]. However, this is also associated with a number of difficulties. Formations often have a complex anatomical location, intimately adjacent to large vascular-nerve bundles, which is due to the mechanism of development of lymphatic vessels from embryonic veins and the location of the primary lymphatic sacs. And the infiltrative nature of the growth of small cystic lymphatic malformations extremely rarely allows for radical removal [9]. This significantly worsens the results of surgical intervention, increases the risk of severe complications and recurrence [9]. The incidence of complications of surgical interventions is 19-33%, the incidence of postoperative relapses is about 12% with visually radical removal and reaches 53% with partial resection.

Drug therapy for lymphatic malformations was initially considered an adjunct to various types of surgical treatment. However, in the last decade, significant advances in understanding the pathogenesis of lymphatic malformations have led to targeted pharmacotherapy becoming increasingly important. Since 2008, the first reports of sirolimus' use in the conservative treatment of lymphatic malformations have emerged. Sirolimus is an immunosuppressant and antitumor agent originally used as an antibacterial agent. Sirolimus acts by inhibiting mTOR kinase, a key enzyme in cell cycle regulation. Inhibition of the mammalian target of rapamycin (mTOR) inhibits the cell cycle at the junction between the quiescent phase and the DNA replication phase. Furthermore, rapamycin inhibits the endothelial cell response to proangiogenic factors, significantly slowing angiogenesis. Sirolimus inhibits VEGF-induced microvascular hyperpermeability. The therapeutic plasma concentration of

the drug is considered to be 10–15 ng/ml. Due to the lack of clinical guidelines and corresponding indications in the instructions for the drug, it is prescribed off-label. Conducted studies confirm the efficacy of sirolimus in stopping lymphorrhea, including in generalized malformations, reducing pain and improving quality of life in patients with lymphatic malformations. However, the effect on overgrowth in the presence of a PIK3CA mutation was not so insignificant [23]. Advances in the detection of genetic mutations and promising results using sirolimus have led to studies on the use of a specific phosphatidyl-inositol 3-kinase inhibitor (alpelisib) as targeted therapy in patients with mutations in the PIK3CA gene.

Conclusion. In the neonatal period, cystic lymphatic malformations can cause complications, necessitating urgent surgical treatment. Therefore, despite the general trend toward conservative treatment, radical removal of the lesion remains the gold standard of treatment for infants. Conservative therapy should only be prescribed if there is no risk of life-threatening complications and if surgery is not possible.

Molecular genetic testing is essential for all patients with cystic lymphatic malformations, as it allows for the earliest possible detection of overgrowth spectrum disorders and the initiation of targeted therapy, which significantly improves the prognosis. All children with a detected mutation should be referred to a pediatric oncologist to determine the need for targeted therapy with a phosphatidyl-inositol-3-kinase inhibitor. Regular follow-up of this group of patients is crucial, as the clinical manifestations of overgrowth spectrum disorders may not be evident at birth, and the presence of a lymphatic malformation may be only the first manifestation of a syndromic pathology.

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