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CHYLOUS ASCITES IN THE NEONATE: A NARRATIVE REVIEW

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ABSTRACT

Chylous ascites (CA), also called chyloperitoneum, is a rare form of ascites in the neonate. It results from the leakage of lymph into the peritoneal cavity. There are congenital and acquired forms of CA. CA may occur during fetal life, and the prognosis will depend on its volume, gestational age at the onset, and the association with other anomalies. Lymphangiectasia is the most common congenital cause, and acquired forms are mainly traumatic and/or post-operative. This review aims to gather the most current information on CA and addresses important aspects regarding etiology, pathophysiology, clinic, diagnostic tools, and treatment.

Keywords: chylous ascites, chylous peritoneum, lymphangiectasia, neonate.

Chylous ascites (CA), also called chyloperitoneum, is a rare form of ascites in the neonate and results from the leakage of lymph into the peritoneal cavity (1). This usually occurs due to trauma and rupture of the lymphatics, increased peritoneal lymphatic pressure secondary to obstruction or lymphatic anomaly. Lymphatic anomaly is the most frequent atraumatic cause in neonates and children (2-4).

CA may occur during fetal life, and the prognosis will depend on its volume, gestational age at the onset, and the association with other anomalies (5). When bulky, the CA may involve some kind of intrauterine procedure in order to avoid a threatening fetal disease. This is mainly if associated with chylothorax where massive pleural and/or peritoneal effusions may impair venous return, cardiac output, and renal flow, allowing massive exit of fluid and protein into the body tissues that become edematous. This situation is known as hydrops fetalis (HF) and can seriously compromise fetal life (5).

This narrative review was performed with the aim of gathering information on neonatal ascites so that it can help the neonatologist in their clinical practice. For this purpose, the most relevant articles available PUBMED and PUBMED CENTRAL databases, with no date limit, were analyzed.

Anatomy and Physiology

Lymph fluid originates in interstitial spaces of the body and transports nutrients including chylomicrons, proteins, cells, hormones, electrolytes, bicarbonate, and sometimes bacteria. Lymph enters the lymphatic system through a network of vessels with unidirectional valves. Lymph is filtered through lymph nodes, which remove various substances (cellular waste, water, proteins) from the interstitial fluid, and house immune cells that continuously sample it and are ready to mount an immune response. The abdominal lymphatic system is also involved in fat absorption from the gut and protection against pathogens. Long-chain triglycerides contained in the alimentary fat are digested in the small bowel and reduced to monoglycerides and

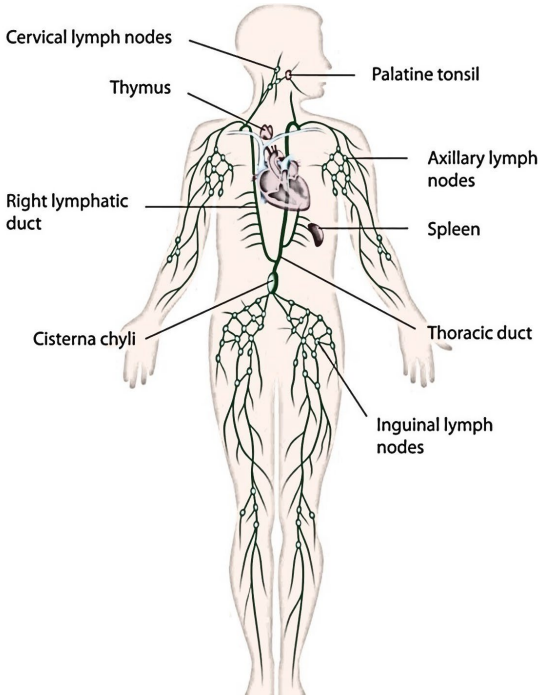

Fig. 1. *The human lymphatic system anatomy depicting channels and regional lymph nodes. Adapted from Knight and Nigam (7).*

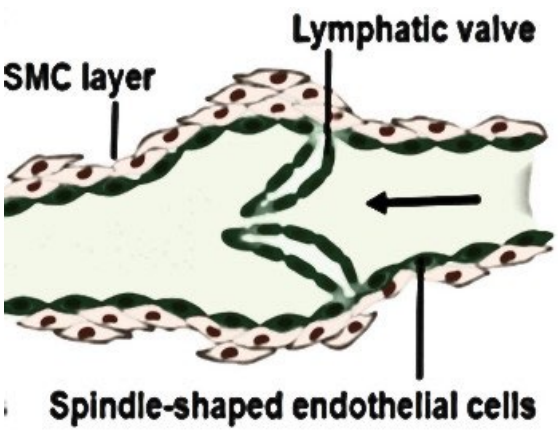

Fig. 2. *Lymphatic vessels contain intraluminal valves (arrow) and smooth muscle cells (SMC) layers that enable the unidirectional lymph flow that eventually empties into the venous system. Adapted from Shang et al. (8).*

fatty acids that are absorbed as chylomicrons and enter the lymphatic vessels. This explains why after feeding, lymph is cloudy and milk-like. Lymph from abdominal organs reaches the lumbar (right, left) and intestinal lymphatic trunks that unite at the cisterna chyli, located between the aorta and the inferior vena cava in front of the first lumbar vertebral body (*Fig. 1*). Lymph then transits the thoracic duct, which ascends in the posterior right mediastinum between the aorta and the azygos vein, crosses to the left behind the aortic arch, and finally opens into the venous circulation at the level of the confluence of the left subclavian and jugular veins (6,7).

Lymph is propelled through its circuit by the active, intrinsic contraction/relaxation of lymphatic vessels and passive, external compressive forces (skeletal muscles, central venous pressure variations, respiratory movement and pulsations of adjacent arteries). Lymphatic vessels also have multiple valves to prevent lymph back-flow (*Fig. 2*) (8,9).

When the lymphatic system, particularly its main conduits, are harmed or obstructed, or present an abnormal anatomy, lymph may leak into the surrounding tissues and can fill the peritoneal space, giving rise to a chylous ascites (1).

Large abdominal lymphatic malformations are rare and may occasionally cause life-threatening illness. This is especially true when they involve the central lymphatic system, lumbar trunks, cisterna chyli, thoracic duct, and their major tributaries and form complex lymphatic anomalies. These large abdominal lymphatic malformations are often accompanied by chylous ascites (10).

Etiologies

There are congenital and acquired forms of CA. Steinemann, et al found lymphangiectasia to be the most common cause of congenital anomaly in children (84%) (11). Primary intestinal lymphangiectasia or Waldmann's disease is characterized by the presence of dilated lymph vessels due to the lack of valves in the submucosa of the small bowel, which

Table 1
Etiologies of Various Conditions with Congenital Forms of Chylous Ascites (Ref. 14).

Disease	Clinical findings	Prevalence
Lymphangiectasia or Waldmann's disease OMIM: 152800	A rare intestinal disease characterized by dilated intestinal lacteals which cause lymph leakage into the small bowel lumen. Clinical manifestations include edema related to hypoalbuminemia (protein-losing gastro-enteropathy), asthenia, moderate diarrhea, lymphedema, serous effusion, and failure to thrive in children. Primary intestinal lymphangiectasia is generally diagnosed before 3 years of age but may be diagnosed in older patients with very few symptoms. The main symptom is predominantly bilateral lower limb edema related to protein-losing enteropathy associated with hypoalbuminemia.	Unknown, less than 500 cases have been reported worldwide
Yellow Nail syndrome OMIM: 153300	A rare, syndromic nail anomaly disease characterized by the variable triad of characteristic yellow nails, chronic respiratory manifestations, and primary lymphedema. Most cases are of late onset, after 50 years of age, but the disease has also occasionally been observed in neonates and children. About one third of the patients with nail changes have associated lymphedema and respiratory tract involvement. Lymphedema is the most consistent associated finding and usually affects the lower limbs. The etiology has not been elucidated; impaired lymphatic drainage not due to anatomical abnormalities, but rather to a functional disorder, appears to have a central role.	Unknown
Klippel–Trenaunay syndrome OMIM: 149000	Capillary and lymphatic hypoplastic malformations, associated with soft tissue and bony hypertrophy, limb asymmetry, hemangioma, venous insufficiency, cellulitis, gastrointestinal hemorrhage, pulmonary embolism, tall stature, and venous thrombosis.	<1 / 1,000,000
Ehlers-Danlos syndrome type VI OMIM: 614557	The Ehlers-Danlos syndrome type VI is an autosomal recessive connective tissue disease which is characterized by severe hypotonia at birth, progressive kyphoscoliosis, skin hyper-elasticity and fragility, joint hypermobility and (sub-) luxations, microcornea, rupture of arteries and the eye globe, and osteopenia.	Unknown
Lymphangiomas	Lymphangiomas are malformations of the lymphatic system characterized by lesions that are thin-walled cysts; these cysts can be macroscopic, as in a cystic hygroma, or microscopic. These malformations can occur at any age and may involve any part of the body, but 90% occur in children less than two years of age and involve the head and neck. There are three distinct types of lymphangioma. They are distinguished by the depth and the size of abnormal lymph vessels: Lymphangioma circumscriptum, a microcystic lymphatic malformation, resembles clusters of small blisters ranging in color from pink to dark red. They are benign and do not require medical treatment, although some patients may choose to have them surgically removed for cosmetic reasons. Cavernous lymphangiomas are generally present at birth but may appear later in the child's life. These bulging masses occur	1-5 / 10,000

	deep under the skin, typically on the neck, tongue and lips, and vary widely in size, ranging from as small as a centimeter in diameter to several centimeters wide. In some cases, they may affect an entire extremity such as a hand or foot. Cystic hygroma shares many commonalities with cavernous lymphangiomas, and some doctors consider them to be too similar to merit separate categories. However, cystic lymphangiomas usually have a softer consistency than cavernous lymphangiomas, and this term is typically the one that is applied to lymphangiomas that develop in fetuses. They usually appear on the neck (75%), arm pit, or groin areas. They often look like swollen bulges underneath the skin.	
Primary lymphatic hypoplasia	Primary lymphedema is a lymphatic system malformation characterized by swelling of an extremity that can be associated with other lymphatic effusions, due to an underlying developmental anomaly of the lymphatic system (abnormal lymphangiogenesis). It can be hereditary or not and be congenital or late onset.	1-5/ 10,000
Chyle cysts	A chylolymphatic cyst is a rare variant of a mesenteric cyst. These cysts present within the mesentery, lined with a thin endothelium or mesothelium and filled with chylous and lymphatic fluid. Although mesenteric cysts in general have been reported in the literature fairly frequently, chylolymphatic cysts in the pediatric age group are extremely rare in the modern medical literature, therefore very little information is available regarding their presentation and complications.	Unknown
Lymphangiomatosis	A rare developmental defect during embryogenesis characterized by multifocal dilated lymphatic vessels involving multiple organs and tissues. Patients mostly present in infancy and childhood. Clinical course and prognosis depend on the affected sites and extent of the condition, deterioration of lung function being a major cause of morbidity and mortality.	Unknown

result in leakage of lymph (12). Waldmann, et al (13) first described this disorder in 1961 as a cause of protein-losing enteropathy, lymphopenia, hypoalbuminemia, and hypogammaglobulinemia.

Other lymphatic anomalies exist, but they constitute a smaller percentage of cases of congenital CA (*Table 1*) (14). For example, yellow-nail syndrome causes CA due to hypoplastic lymphatics and consists of the triad of lymphedema, pleural effusion and/or CA and yellow discoloration with nail dystrophy (15). The Klippel-Trenaunay syndrome is an inherited autosomal dominant disorder that is characterized by capillary and lymphatic hypoplastic malformations that causes CA and is associated with soft tissue and bony hypertrophy (16-18). A case of congenital CA associated with Ehlers-Danlos syndrome type VI, probably due to primary lymphatic defect with additional vascular anomaly, has been described in a 35-day-old male (19). Lymphangiomas arise from the sequestration of lymphatic tissue, which fails to communicate with the lymphatic system and can reside in the neck, intestine, pancreas, or mesentery (20,21). Primary lymphatic hypoplasia, chyle cysts, or lymphangiomatosis have also been described in association with CA (22).

Acquired forms of CA are mainly traumatic and/or post-operative (1). Acquired forms may occur after the obstruction of the

thoracic duct or as a rare complication of peritoneal dialysis, probably due to trauma to the lymphatic system with dialysis catheter placement (23-25).

CA has been described after primary surgical repair of esophageal atresia with tracheoesophageal fistula. This probably resulted from iatrogenic damage of the thoracic duct during the ligation of azygous vein, resulting in leaking lacteals within the intestinal wall (26). CA has been described after congenital diaphragm hernia repair (27). A neonate who had an uncomplicated repair of gastroschisis with modified Ladd's procedure developed CA when fed (28). A late post-repair CA developed in an unusual case of gastroschisis with gallbladder evisceration (29). A CA was described in association with malrotation of the intestines (30). Seltz, et al (31) describe a neonate with a CA caused by intestinal malrotation associated with heterotaxia syndrome. A cardiothoracic surgery or procedure may injure the thoracic duct and lead to chylothorax. However, there are very few reported cases of isolated CA developing following cardiothoracic surgery. A case of postoperative CA in a full-term neonate that underwent cardiothoracic surgery via thoracotomy to repair a total anomalous pulmonary venous connection has been described (32). CA can occur early (around 1 week) after abdominal surgery due to the disruption of the lymphatic vessels, or late (weeks to months), due to adhesions or extrinsic compression of lymphatic vessels (33). Asymptomatic chylous ascites have also been found in neonates and children operated for inguino-escrotal hernia (34). Malignancies, such as spinal cord gliomas and neuroblastoma have a predilection to invade the posterior mediastinum and may lead to both chylothorax and CA (35-38).

Clinical Findings

Abdominal distension, along with weight gain, are the most common presenting findings when there is no antenatal diagnosis of ascites. Patients that underwent an abdominal or thoracic surgery may present with an acute onset of CA. A concomitant chylothorax may occur after a thoracic surgery. Dyspnea, resulting from increased abdominal girth, may become a problem and even require some kind of ventilator support or hinder the extubation of ventilated patients (39).

The increased pressure in the abdominal cavity may cause discomfort or even pain, depending on the volume, vomiting, inguinal hernias, scrotal or vaginal edema (40). Abnormal function of the gastrointestinal tract results in malabsorption of nutrients in the intestines (41).

Lymphatic fluid loss into the peritoneal cavity is associated with the loss of key elements such as lymphocytes, immunoglobulins, chylomicrons, several small molecular weight proteins, coagulation factors, hormones, electrolytes, bicarbonate, and fluid. The significant loss or drainage of these elements puts the patient at risk for hypovolemia, hypotension, malnutrition, hypoproteinemia, coagulation problems, electrolyte imbalance, metabolic acidosis, lymphocyte depletion, hypogammaglobulinemia, immune deficiency, and increased risk of infections (42,43).

Diagnosis

CA is readily detected by imaging soon after clinical onset. It is then necessary to obtain and analyze an ascitic fluid sample for confirmation (3). The sample is usually collected by abdominal paracentesis. More rarely, the sample can be collected after placement of an abdominal drain or it can be collected in a laparotomy performed for another reason in an asymptomatic patient The diagnosis of CA is confirmed when the analysis of peritoneal fluid shows a cell count greater than 1000 white blood cells per µL, with more than 70%-80% lymphocytes and, in enterically fed patients, a triglyceride concentration greater than 110 mg/dL (1.1 mmol/L) (1,3,32,44-46).

Fetal ascites may be diagnosed as early as 14 weeks of gestation during ultrasound screening, and follow-up with ultrasound will identify its progress and if hydrops fetalis develops. If signs of hydrops (pleural or pericardial effusion, fetal subcutaneous edema) are detected along with ascites, further urgent in-

vestigations including maternal serologies for TORCH infection, Rhesus factor and blood group antibodies, amniocentesis for karyotyping, and fetal echocardiography need to be carried out to detect the underlying etiology (47,48). On the other hand, in the presence of isolated fetal ascites, associated anomalies of heart, gut, and urogenital should be examined (49). Fetal cordocentesis can add on to identifying the etiology of ascites in 92% cases as reported by Schmider et al (48). If ascites increases significantly, fetal paracentesis may need to be carried out to improve lung growth and prevent pulmonary hypoplasia in neonatal development. Moreover, it may avoid abdominal dystocia if vaginal delivery is planned (49).

Imaging

An anteroposterior abdominal radiograph may show peripheral and inferior accumulation of fluid with central agglomeration of airy bowel loops. An abdominal ultrasound allows confirmation of intraabdominal fluid as well as quantifying its volume. In cases of lymphatic obstruction, lymphangiography and lymphoscintigraphy are important diagnostic tools in detecting abnormal retroperitoneal nodes, leakage, fistulation, and patency of thoracic duct (1,50,51). Computed tomography and magnetic resonance imaging are not specific for CA, but they are useful in identifying intraabdominal masses and lymph nodes (1,52).

Fluoroscopic intranodal lymphangiography with injection of oil-based contrast material into groin lymph nodes improves visualization of central conducting lymphatics (CCLs) but is limited in practice, owing to the use of radiation and the potential risk for paradoxical embolization in children with left-to-right shunt. Dynamic contrast material-enhanced (DCE) magnetic resonance lymphangiography, which is performed by injecting gadolinium-based contrast material into groin lymph nodes, overcomes these limitations. T2-weighted imaging plays a complementary role to DCE magnetic resonance lymphangiography in the assessment of CCLs. DCE magnetic resonance lymphangiography demonstrates preserved integrity or any abnormality of the CCLs (including blockage or leak). The technique has recently been used in evaluating pulmonary lymphatic perfusion syndrome in children with plastic bronchitis, neonatal lymphatic flow disorders, and nontraumatic chylothorax. It is useful in the identification of the source of CA and contributes to the understanding of the anatomy of lymphatic malformations. It is successfully used for planning of embolization of aberrant lymphatic channels in a variety of lymphatic flow disorders (53).

Treatment

The treatment of CA should be individualized according to its severity and the clinical condition of the patient (33). The heterogeneous clinical presentation of CA, numerous etiologies, its rarity, difficulties in using diagnostic image techniques in small neonates, and the absence of a highly effective treatment render the treatment of CA difficult to standardize. The goal of the treatment of a lymphatic peritoneal effusion is to decrease its volume and to allow time for the injured lymphatic vessels to heal or develop.

Antenatally detected large fetal ascites may necessitate abdominal paracentesis and amnioreduction and marked respiratory distress at birth requires urgent abdominal paracentesis to relieve symptoms (54).

After birth, treatment begins with supportive management, including nutritional management, pharmacological reduction of intestinal chyle production, respiratory support, peritoneal paracentesis or drainage, cardiovascular support, and pain therapy. Along with these steps, it is important to avoid, or at least minimize, the risk of malnutrition, hypoproteinemia, electrolyte imbalance, metabolic acidosis, coagulation problems, lymphocyte depletion, hypogammaglobulinemia, immune deficiency, and infections (3,33,45,54).

The nutritional management includes bowel rest and total parenteral nutrition (TPN), or a medium-chain triglycerides (MCT) diet (Monogen®; Portagen®;

Enfaport®) or fat-modified breast milk; breast milk can be centrifuged and converted into low-fat breast milk, which can be supplemented with MCT (54-58). TPN and bowel rest decrease chyle flow in patients who fail to respond to the MCT diet (54,59). MCT diet is absorbed directly into the portal system, rather than through lymphatics. Dietary management should be continued for at least 10 weeks, before a possible surgical intervention is considered (60). Some authors suggested that a surgical approach should be attempted after two months of ineffective conservative care (61,62). The neonate with occluded thoracic duct needs weeks to months for developing alternative lymphatic routes (3).

In addition to the nutritional approach, volume replacement with colloids such as albumin (5%), to prevent hemodynamic imbalance of drainage or repeated paracentesis, should be performed (54).

Octreotide, a synthetic analogue of somatostatin that has been used as an adjunctive therapy to reduce splanchnic flow and thus portal pressure, inhibits intestinal fat absorption and lymphatic flow in the thoracic duct (63,64). Octreotide is generally used as the first-line treatment for chylous effusions (3). It is usually started with 1 mcg/kg/hour IV continuous infusion and titrated upward as necessary based on reduction in chyle production to a maximum dose of 10 mcg/kg/hour. Higher doses can increase the risk of necrotizing enterocolitis in the neonate (65). The dosage is increased by1 mcg/kg/hour every 24 hours. To stop the treatment, infusion is decreased gradually over 2 to 7 days. It can also be used subcutaneously or IV in divided doses every 6 hours (66).

Etilefrine, a sympathomimetic drug used in the management of postural hypotension, also causes smooth muscle contraction of the thoracic duct and has been successfully used to treat chylothorax and CA in adult patients (67,68). It has also been used to treat chylothorax in pediatric patients (69,70).

With significant losses or high-volume drainage of lymph from the peritoneal cavity, the infant may become depleted in immunoglobulins, lymphocyte, bicarbonate, coagulation proteins, and electrolytes (1). It is advised that lymphocyte count and serum immunoglobulins in patients with prolonged and/or high-volume drainage be monitored, and that the administration of IV Ig be considered (1). It is advised that coagulation and antithrombin in patients with prolonged and/or high-volume drainage be monitored and that antithrombin substitution be considered to prevent thrombotic complications and to optimize heparin therapy in children requiring anticoagulation (71). Blood gas acid-base metabolism should be monitored in patients with prolonged and/or high-volume drainage, and solutions containing bicarbonate should be administered in case of metabolic acidosis (72).

Midodrine, an oral alpha-1-adrenoreceptor agonist, achieved remission of congenital chylous pleural effusion and ascites in a neonate, without any adverse effects (73).

Propranolol, commonly used for treatment of infantile hemangiomas, is currently gaining interest as a novel therapy for chylous effusions, including CA (74).

If the conservative management is not successful in treating CA, surgical intervention may be beneficial and/or curative. In congenital forms of CA, lymphangiography or lymphscintigraphy may identify the location of the leakage or the presence of a fistula (50,51). Lymphangiography with embolization with lipiodol, or other products, may lead to the resolution of lymphatic leakage and has already been successfully used in an extremely-low-birth-weight infant girl who developed a chylothorax that was refractory to medical treatment (75). Neville J, et al summarized the outcomes following lymphangiography and/or interventions in neonates (under two months) with primary or post-operative chylothorax or CA (76). A laparotomy may be essential in the diagnosis and treatment of congenital forms for fistula closure, bowel resection when lymphangiectasias are localized to a segment of the bowel, or insertion of a peritoneovenous shunt for generalized lymphatic malformations (39,77-80). Surgical correction of lymphatic obstruction from intestinal malrotation, mesenteric cysts, and hernias is also effective in promoting resolution of CA (81). The use of

fibrin glue over the leaking intestinal lymphatics may lead to the resolution of the CA (82).

When the CA results from trauma to the thoracic duct during a thoracic or a cardiothoracic surgery, a chylothorax is usually present. Invasive possibilities for treatment are the same as those used in traumatic chylothorax and include thoracic duct ligation, pleurodesis, thoracic duct embolization, fibrin glue, and lymphovenous anastomosis (83).

Prognosis

The prognosis of CA is generally favorable in acquired/traumatic forms. In congenital forms, prognosis depends on the severity and extent of lymphatic abnormalities, presence of other associated congenital abnormalities, and severity of the patient's overall status.

CONCLUSIONS

CA is an uncommon disorder in the neonate. The most common etiologies are lymphatic anomalies or traumatic causes. Congenital forms may occur isolated or associated with other congenital anomalies or as a part of a genetic syndrome. The diagnosis is based on paracentesis and ascitic fluid analysis. Conservative treatment with nutritional optimization and treating the underlying etiology remains the cornerstone of therapy. With significant losses, or high-volume drainage of lymph from the peritoneal cavity, the infant may become depleted in immunoglobulins, lymphocyte, bicarbonate, coagulation proteins, and electrolytes. Octreotide has been used as an adjunctive therapy to reduce the splanchnic flow. Lymphangiography and lymphoscintigraphy are important diagnostic tools but require experience as well as lymphatics embolization. When a lesion that can be corrected by surgery is apparent, a laparotomy should be performed. In a few cases of CA, peritoneovenous shunting has been used with good results.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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