Case Report

Journal of Kathmandu Medical College, Vol. 12, No. 2, Issue 44, Apr.-Jun., 2023

Congenital chylothorax in a preterm infant with non-immune hydrops: A case report with literature review on treatment options

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Abstract

Congenital chylothorax is rare with an incidence of 1:10,000-24,000 live births. Congenital chylothorax occurs in lymphatic disorders, heart diseases, cancers, chromosomal abnormalities, tracheoesophageal fistula, etc. Acquired causes are due to surgical thoracic duct trauma. Many cases of chylothorax are idiopathic. The case fatality rate is 15% to 57% and reaches 98% in hydrops foetalis. There is no set standard of treatment for congenital chylothorax. Prenatally, thoracentesis or pleuro-amniotic shunts are done. Postnatally, management of cause, drainage, dietary changes, Octreotide, and Sildenafil have variable results. Pleurodesis, pleuroperitoneal shunt, abrasion, thoracic duct ligation, and anastomoses are surgical options.

Key words: Congenital chylothorax; Hydrops foetalis; Octreotide; Sildenafil.

INTRODUCTION

Congenital chylothorax (CC) is a rare condition that affects males twice as often as females and more frequently on the right side.[1] The CC is seen with lymphatic abnormalities, mediastinal disorders, and genetic abnormalities. Many cases of CC are idiopathic.[2] Case fatality rate reported is 15% to 57%.[3,4] A guideline for the management of CC is still not definitive.[5] Many antenatal and postnatal interventions have been tried with varied success rates. Here, a case of hydrops foetalis with CC is presented, that was successfully treated with chest tube drainage, octreotide, and sildenafil. Literature review with treatment modalities has been discussed.

Access this article online

Website: www.jkmc.com.np

DOI: https://doi.org/10.3126/jkmc.v12i2.60349

HOW TO CITE
Raya GB, Basnet S, Nyaupane S. Congenital chylothorax in a preterm infant with non-immune hydrops: A case report with literature review on treatment options. J Kathmandu Med Coll. 2023;12(2):116-22.

Submitted: May 08, 2023
Accepted: Jun 23, 2023
Published: Jun 30, 2023

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ISSN: 2019-1785 (Print), 2091-1793 (Online)

CASE REPORT

This is a case report of a male baby with congenital chylothorax, born to 32 years old mother at 32 weeks and five days of gestation. The mother had a history of one abortion, a neonatal death with hydrops foetalis, and a living healthy girl of eight years. The marriage was non-consanguineous. The mother had no known medical condition. Her blood group was B positive and had normal thyroid, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and human immunodeficiency virus (HIV) screening (TORCH panel test), and blood sugar profiles. Tests for Hepatitis B and C were negative. She was regularly taking Iron and Calcium supplements apart from Vitamin D for the low levels of the vitamin.

Ultrasonography (USG) done at six weeks of pregnancy showed normal findings. A foetal echocardiogram performed at 32 weeks of gestation was normal. There

were no clinically remarkable events until 36 weeks of gestation when USG abdomen revealed breech presentation, polyhydramnios [Amniotic Fluid Index (AFI) 26.4], foetal pleural effusion, and scalp oedema. The pleural effusion was gross on the right and moderate on the left. The Doppler study on the middle cerebral artery, and the umbilical artery were normal. No ascites was noted. The estimated foetal weight was 2963 grams.

The baby (Figure 1), delivered through a caesarean section, did not cry at birth and required endotracheal intubation. Mechanical ventilation in the neonatal intensive care unit (NICU) required higher peak pressures. He was supported with dopamine, amino acids infusion along with usual intravenous maintenance fluid, and was kept nil per oral. The baby had no syndromic features but had generalised oedema of the body. The first chest roentgenograph showed bilateral homogenous opacity over the entire lung field suggestive of pleural effusion (Figure 1). There was minimal aeration on the left lung field.

Immediate chest tube insertion was done bilaterally, and 120 ml of straw-coloured fluid was drained. Initial lab investigation on the pleural fluid revealed total white cell counts of 6300 cells per microlitre with 97% lymphocytes, 75mg/dL of sugar, and 3.8 gm/L of proteins. The Gram stain and acid fast bacilli stain were negative.

The baby remained stable in the NICU with mechanical ventilation. The initial total blood cell counts were 19600/µL with 34% neutrophils, 64% lymphocytes, platelets 281000/µL, and haemoglobin was 14.2g/dl. The blood group was A positive. Reticulocytes was 5.3% with immature to total leukocytes (IT) ratio 0.08, and C-reactive protein <6 mg/L. Liver and renal functions were within normal limits. The blood smear showed normochromic, normocytic red blood cells (RBCs) with several polychromatophils and nucleated RBCs. Initial arterial blood gas (ABG) showed metabolic acidosis with hypoxaemia which was later corrected. The USG abdomen pelvis confirmed bilateral pleural effusion (right moderate, left minimal) - otherwise normal. Echocardiography showed a secundum atrial septal defect (ASD) measuring 2.3 mm which was shunting left to right. There was normal left ventricular contractility (left ventricular ejection fraction = 65%) and mildly elevated pulmonary artery pressure. No superior venacaval obstruction was noted.

Extended metabolic screening (tandem mass photospectrometry) was normal. Karyotype was 46, XY.

Without oral fat intake, chylomicrons are absent in the pleural fluid and hence it is clear; the diagnosis of chylothorax is made by identifying the presence of a high number of lymphocytes in the serous fluid.[6] In view of bilateral pleural effusion and generalised body oedema with no immunological cause found, congenital chylothorax with non-immune hydrops was the provisional diagnosis.

Continuous water-sealed drainage was maintained, 110 ml and 100 ml of clear fluid was drained on the first and second days respectively. The lung fields were gradually aerated (Figure 2). Pneumothorax occurred twice and was managed by repositioning the chest tubes. The left chest tube was removed on the eighth day and the right, on the ninth day of insertion.

Oral feeding started followed by breast-feeding. With the gradual onset of respiratory distress, a chest X-ray confirmed the collection of fluid in the right pleural space. Reinsertion of the chest tube on the right side yielded whitish fluid, the analysis of which showed a triglyceride level of 3.5 mmol/L. According to the well-accepted guideline for diagnosis of chylothorax in children, pleural effusion in children is chyle when it contains >1.1 mmol/L triglycerides (with oral fat intake) and has a total cell count >1,000 cells/µL, with a lymphocyte fraction >80%.[7] Hence chylothorax was confirmed. Then oral milk feeding was stopped. Median chain triglyceride (MCT) oil and vitamin supplements were given orally; amino acids infusion with maintenance fluid was continued. Preparation for total parenteral nutrition could not be made available. Octreotide was started intravenously and gradually escalated up to 7 µg/kg/hr.

A computed tomography (CT) chest showed right pleural effusion with fissure extension and basal atelectasis of the right lower lobe of the lung. Thoracic surgical evaluation recommended for conservative management. Oral sildenafil was added, and the dose increased up to 1 mg/kg/day in three divided doses. During dual drug therapy there was no drug related complications noticed. The drainage was significantly decreased to 30 ml/day on the third day and nil on the fourth day of dual therapy. The Inj. Octreotide was tapered off over three days. Enteral feeding was given only for MCT based formulas and multivitamins supplements. Amino acids and dextrose infusion were given in usual maintenance dose with replacement of chest drain fluid. Breast feeding was reintroduced two days after stoppage of octreotide infusion. As no further pleural effusion was noted with gradual improvement on clinical status, the chest tube

drainage was removed on the 10th day of the reinsertion. The baby was discharged on sildenafil, which was tapered off gradually over the next one month.

On the 72nd day of life, the baby was again seen in the follow-up outpatient clinic. Breast-feeding was well, there was no issue reported. The baby was thriving. Chest X-ray on follow-up was grossly normal with minimal effusion on the right (Figure 3).

DISCUSSION

A mismatch between the lymphatic return and interstitial fluid generation results in hydrops foetalis. In congenital chylothorax, non-immune hydrops foetalis (NIHF) results from an increase in central venous pressure due to venacaval obstruction or decreased cardiac function by the effusion.[8]

The spontaneous postnatal resolution over a few days is a part of the natural history of CC.[6] With the widely varied clinical course, the modalities of measures for non-resolving chylothorax have not yet been well defined.[1] The neonatal treatment strategy is generally supportive with interventions to decrease chyle flow. While there is a dearth of evidence-based treatment guidelines, most cases of CC resolve over time even in the absence of particular lymphatic system evaluation and treatment.[9]

Conservative treatment is typically the first choice due to its high success rate (75–80%).[3] It is recommended that surgical treatment should be delayed 4-5 weeks after the diagnosis.[3,7] Selles et al.[10] recommend surgery rather than conservative treatment whenever the daily output of chylous fluid is more than 100 ml per year of age in children for more than five days or an ongoing chyle flow for two weeks.

Conservative management includes treatment of the cause, thoracenteses, chest tube drainage, dietary modification, chemical, and mechanical pleurodesis whereas thoracoscopic pleurodesis, pleuroperitoneal pump drainage, surgical abrasion, thoracic duct ligation, thoracic duct to azygos vein anastomosis are surgical approaches.[4]

Antenatal interventions: Prenatal treatment in foetuses <34 weeks of gestation with CC have better postnatal outcomes. Lee et al. described 29 such cases having a significantly higher survival rate in the prenatal treatment group, compared to infants who did not receive prenatal

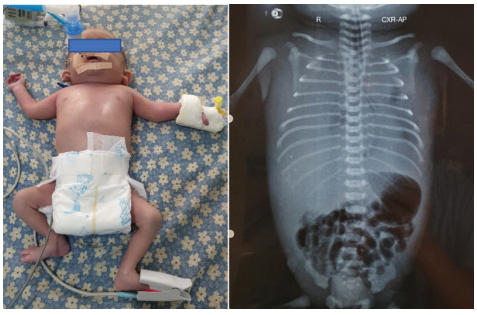

Figure 1: **The first chest X-ray of the baby showing bilateral hydrothorax**

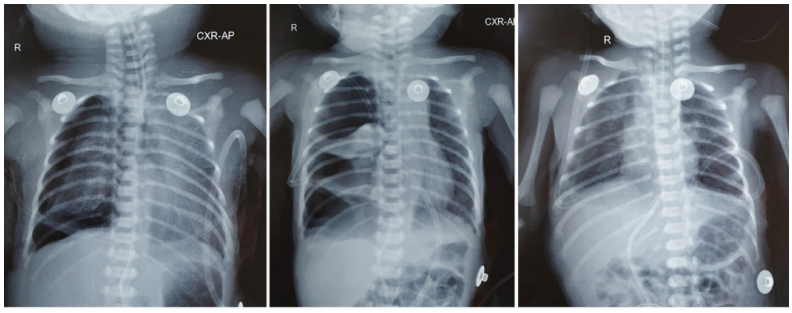

Figure 2: **Serial chest X-ray films showing gradual improvement in the lung fields aeration after bilateral chest tube insertion**

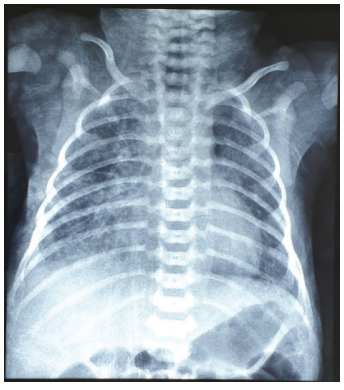

Figure 3: **Chest X-ray on follow-up**

therapy (76.9% vs. 11%, respectively; p = 0.008). A change in the mother's diet, recurrent thoracentesis, thoraco-amniotic shunting, and pleurodesis with OK-432 were among the prenatal treatment measures.[8] Bartha and Camino have reported a case[11] with congenital chylothorax where they claim that introducing a low fat and high MCT diet to the mother decreases the estimated volume of chylous pleural effusion from 78 ml to 57 ml in seven days. For severe or recurring chylothorax, a percutaneous in utero pleuro-amniotic shunt is performed to allow lung development and prevent heart failure.[8] Case series have shown that reinsertion of the shunt was required in 6–8%, and foetal loss was around 10%. In a study[12] done with 78 foetuses, each foetus had an average of 2.53 shunts (1-7) implanted. Forty-six (59%) survived, 69 (88.5%) were born alive, and 9 (11.5%) died in utero. Installing OK-432 (Picibanil, Chugai Pharmaceutical Co., Tokyo, Japan - a lyophilised preparation of a low-virulence human strain of group A Streptococcus pyogenes as a sclerosing agent for foetal pleurodesis has been described with no recurrence of effusion following complete aspiration of pleural effusion and ultrasound demonstration of adhesions.[13]

Postnatal management: Total parenteral nutrition with octreotide perfusion (1 mcg/kg/h increasing daily up to10 mcg/kg/h), followed by re-establishment of feeds using an MCT-based milk formula is recommended.[1] Drainage should be less than 10 ml/kg/day within a week; else, more drastic treatments should be taken.[8] To maintain proper lung expansion and prevent the fluid from reaccumulating, ventilatory support will be needed for the majority of newborns who are born with substantial chylothorax. High frequency ventilation has been proven to be beneficial.[8]

Dietary modification: Given that human milk contains a significant amount of long-chain fatty acids, chylothorax is seen as a contraindication to breastfeeding.[14] Completely depriving babies with CC of breast milk is detrimental to neurological development as the growing brain essentially needs balanced nutrition of fatty acids. The chyle flow is decreased by MCT-based nutrition that contains enough long-chain fatty acids.[5] Peitersen and Jacobsen, however, found that total parenteral nutrition is better than MCT-rich formula feeds.[14]

Höck et al. have tested fat-modified (skimmed) breast milk to the babies with CC. Skimmed breast milk is prepared by centrifugation at approximately 3000–3500 rpm for 15 mins or by placing the milk in the refrigerator for 4-6 hours until the fat fraction separates. Less than 0.1% of long-chain fatty acids are present in skimmed milk, which means there are fewer calories, important fatty acids, and fat-soluble vitamins.[5] However, it retains normal levels of electrolytes, protein, and lactose, and thus, it is still immunologically active. While another patient experienced a relapse, one patient had no pleural effusion at all.[5] Additionally, newborns with skimmed milk failed to lengthen or gain weight for six weeks.[15] In a study done by Chan and Lechtenberg, after one month of age, the fat-free milk was introduced to seven infants with chylous pleural effusions for an average of 16 days (seven to 34 days range). There was no reaccumulation of the chylous pleural effusion.[16]

Octreotide: This somatostatin analogue, is a relatively safer and important treatment modality in CC with hydrops foetalis.[17] By lowering gastric, intestinal, and pancreatic secretions as well as hepatic venous pressure and splanchnic blood flow, octreotide lessens lymphatic flow.[2] Administered either subcutaneously or intravenously, an intravenous dose range between one and 10 µg/kg/h, and occasionally up to 20 µg/kg/h is most commonly used.[19]

A study done in Thailand reported successful treatment of congenital chylothorax with Octreotide as the first line treatment without dietary modification.[20]

The Cochrane review[6] done by Das and Shah, showed that no randomised controlled trials with the use of octreotide in CC were identified. Four of the 19 case reports of 20 neonates described failure with the use of octreotide, whereas 14 described satisfactory resolution of chylothorax. One report showed equivocal results. Between the second and 109th day after birth, octreotide was given subcutaneously or intravenously. The intravenous infusions were between 0.3 and 10 µg/kg/hr, while the subcutaneous dose varied from 10 to 70 µg/kg/day administered every six hours to 24 hours. Successful treatments lasted somewhere between four days and 21 days. There have been cases of temporary hypothyroidism, necrotising enterocolitis, and intestinal intolerance. According to the review, the medication octreotide may help babies with chylothorax recover more quickly.

Another systematic review done by Bellini et al.[21] found that octreotide was efficacious in 47% of patients, with a modest but insignificant variation in efficacy between congenital chylothorax (30/57; 53.3%) and acquired chylothorax (9/27; 33.3%) (p = 0.10). The most common therapeutic dose ranged from 1-10 µg/kg/h. Vass et al. recommend that a higher dose of octreotide, up to 20 µg/kg/h, is needed in cases of refractory CC.[19] Side effects

were reported in 12 of 84 patients (14.3%). The authors came to the conclusion that octreotide is a generally safe and effective therapeutic choice for infant chylothorax, particularly the congenital types.

Octreotide use has been associated with adverse reactions including flushing, nausea, vomiting, diarrhoea/constipation, transient hypothyroidism, abnormal liver function, transient abdominal distension, hyperglycaemia/hypoglycaemia, and necrotising enterocolitis.[22] Reports of persistent pulmonary hypertension, cholelithiasis, retinopathy, arrythmia, injection site pain, dizziness and fatigue[6] have also been published.

Sildenafil: Recently, oral sildenafil has been reported to be effective in chylothorax due to non-pulmonary lymphatic malformations in infants and young children.[34] Sildenafil helps lymphatic vessel growth and/or remodelling allowing resolution of lymphatic obstruction. Malleske and Yoder[25] have reported a case where a near term female baby with CC was treated successfully after octreotide failed. On day 15, the infant received parenteral nourishment and then fat-free breast milk. Beginning on day nine of life, octreotide was titrated to a maximum dose of 20 g/kg/hr by day 22. On day 23, the baby was started on oral sildenafil since the chylothorax persisted. Over a two-week period, octreotide was tapered off. Within 15 days of beginning sildenafil therapy, the chylothorax cleared, and by 18 days, all chest tubes had been withdrawn.

Surgical therapy: After four weeks, pleural drainage at a rate of 10 mL/kg/day is deemed to have failed the conservative course of treatment.[26] Long-term ineffective conservative treatment may result in serious immunological and nutritional problems and an extended hospital stay. Surgical options include thoracoscopic pleurodesis, pleuroperitoneal shunt, thoracic duct ligation (by thoracoscopy or thoracotomy), thoracic duct embolisation, thoracic duct to azygous vein anastomosis, and lung transplantation. Chemical pleurodesis with povidone-iodine, tetracycline, talc, bleomycin, and fibrin glue, OK-432 have been reported.[8]

Pleurodesis by povidone-iodine (PI) appears to be well-tolerated and may represent a good alternative to mechanical abrasion or surgery. Brissaud et al. have described four cases of congenital chylothorax treated with PI. One of the cases was refractory to repeated thoracentesis and parenteral nutrition, responded to intrapleural instillation of povidone-iodine. Undiluted Betadine 4% scrub was used in three cases and one case, Betadine 10% Dermique was used diluted with normal saline (3 ml Betadine 10% Dermique +7 ml saline). The chest tube was removed after 16 days of Betadine instillation, with full recovery and a normal thyroid profile both before and after instillation. The amount of PI that was administered ranged from 3-10 ml, and the occlusion time for the chest tube was 2-5 hours. Fentanyl and sufentanil were used for analgesia and Midazolam for sedation. Three of the babies had successful outcomes. Acute renal insufficiency is a well-known effect of povidone-iodine intoxication, particularly in patients with chronic renal failure.

There have been reports of successful uses of intrapleural injections of autologous blood treatment for pulmonary lymphangiectasia.[27] Blood incites an inflammatory reaction in the pleural cavity resulting in adhesion between the parietal and visceral pleurae and has a direct mechanical sealing effect

Case reports of effective successful use of OK-432 in neonatal chylothorax refractory to conservative management have been made.[15] Fever lasting for 2–4 days and a local inflammatory reaction lasting 3–7 days are the reported side effects. Another sclerosing agent oxytetracycline with 2% lignocaine has been reported to be successful when administered into the pleural cavity (on day 20) at a dose of 20 mg/kg through the intercostal drainage (ICD), and the ICD was clamped for two hours. No ICD drainage was noted after two days.[29]

Two infants of post-operative chylous leaks have been reported to be treated successfully with percutaneous thoracic duct embolisation using n-butyl cyanoacrylate diluted 1:2 in ethiodised poppy seed oil.[30]

CONCLUSION

Nepal, a developing country, still lacks skilful manpower for prenatal intrauterine interventions, though this is becoming a possibility recently. Octreotide, sildenafil, dietary modification with MCT oil, and pleurodesis are modalities that any tertiary level hospital in Nepal can adopt.

Conflict of interest: None.
Source(s) of support: None.

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