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PERINATAL/NEONATAL CASE PRESENTATION

Congenital chylothorax treated with oral sildenafil: a case report and review of the literature

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Congenital chylothorax (CC) can result from a congenital malformation or an acquired obstruction or disruption of the thoracic duct. Recently, oral administration of the phosphodiesterase-5 inhibitor, sildenafil, was reported to be effective in resolving non-pulmonary lymphatic malformations in infants and young children. We report a case of CC in a late preterm infant with congenital pulmonary lymphangiectasia where octreotide was not effective, but management with oral sildenafil was successful.

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INTRODUCTION

Congenital chylothorax (CC) can result from a congenital malformation or an acquired obstruction or disruption of the thoracic duct.[1] CC accounts for 15 to 19% of neonatal pleural effusions and has a mortality rate of approximately 33%.[1,2] A variety of approaches are used in managing CC including prolonged hyperalimentation, fat-free feedings and chemical or surgical pleurodesis.[2] Recently, oral sildenafil, a specific inhibitor of phosphodiesterase-5, was reported to be effective in resolving non-pulmonary lymphatic malformations in infants and young children.[3,4] We report a case of CC in a late preterm infant with congenital pulmonary lymphangiectasia where octreotide was not effective, but management with oral sildenafil was successful.

CASE REPORT

A 3281 g female neonate was born at 36 and 5/7 weeks gestation via induced vaginal delivery to a 34-year-old G3 P1001 mother. Maternal serologies were unremarkable, blood group was O+ and red blood cell antibody screen was negative. Maternal medical history was significant only for atopic disease and a first trimester spontaneous abortion. A fetal ultrasound at 19 weeks gestation was normal. Follow-up ultrasound 10 days prior to delivery revealed a fetus large for dates with bilateral pleural effusions and polyhydramnios. Delivery was induced for progressive non-immune hydrops fetalis.

Apgar scores were 1 at 1 min and 8 at 5 min. The infant was intubated at delivery for respiratory failure and placed on high frequency ventilation. A chest radiograph revealed coarse, reticular interstitial markings and bilateral pleural effusions, left greater than right. Bilateral chest tubes were placed and pleural fluid analysis was consistent with chyle. The physical examination revealed moderate generalized anasarca but no syndromic features. Pulmonary hypertension was diagnosed based on persistent hypoxemia requiring a high FiO2 and treatment with 20 ppm of inhaled nitric oxide was initiated. Hematologic, infectious, cardiac, renal and hepatic etiologies for the hydrops and pleural effusions were investigated but were not identified. Chromosomal analysis revealed an isodicentric chromosome 15, but this is not known to be associated with chylothorax.

Parenteral nutrition was provided until fat-free breast milk or Enfaport was introduced on day 15. Octreotide was started on day of life 9 and titrated to a maximum dose of 20 mcg kg^{-1} h^{-1} by day 22. The chylothorax persisted and the infant's course was complicated by multiple chest tube obstructions, hypoproteinemia, hypogammaglobulinemia treated with intravenous immunoglobulin and inadequate nutrition. The infant was extubated to nasal continuous positive airway pressure on day of life 22.

A chest computed tomography scan obtained on day of life 15 demonstrated mild, asymmetric, septal thickening throughout most of the right lung consistent with congenital pulmonary lymphangiectasia. Pulmonology and surgical consultation agreed with the diagnosis. The parents declined an open lung biopsy and on day of life 23 the infant was started on oral sildenafil with the plan to continue treatment for 20 weeks as recently described for the treatment of lymphatic malformation.[3] Octreotide was weaned off over a 2-week period. The chylothorax resolved within 15 days of initiating sildenafil treatment, all chest tubes were removed by 18 days, and the infant was weaned from nasal continuous positive airway pressure to room air by 19 days. Subsequent chest radiographs and CT scans of the chest (Figure 1) demonstrated marked improvement in the lung interstitial spaces and the pleural effusions never reaccumulated.

DISCUSSION

This is the first reported use, of which we are aware, of sildenafil for the management of CC. Sildenafil is an established treatment for pulmonary hypertension in newborns and infants[5] and has recently shown promise as a treatment for lymphatic malformations.[3] Our patient had bilateral CC suspected to be due to congenital pulmonary lymphangiectasia.

CC occurs in about 1/15,000 live births, is the most common cause of congenital pleural effusion and has a mortality rate of 25 to 50%.[1,2] CC is often idiopathic but can be associated with chromosomal abnormalities (most often Noonan, Turner and Down syndromes) or with lymphatic obstruction.[1,2,6] Our patient

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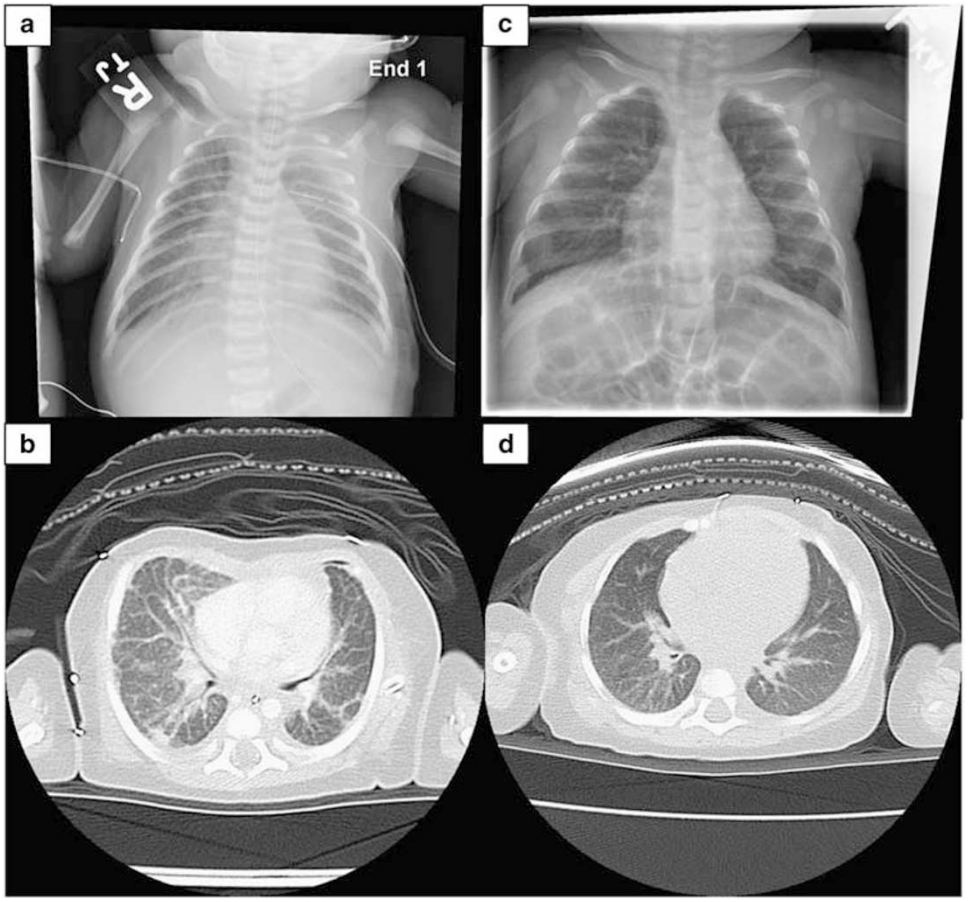

Figure 1. Chest radiographs (**a** and **c**) and CT scans (**b** and **d**) comparing lung images at the start (**a** and **b**) and after 20 weeks (**c** and **d**) of oral sildenafil treatment. Marked improvement is evident in the interstitial and perihilar spaces of the lung fields, and the pleural effusions have resolved.

had a suspected lymphatic malformation, pulmonary lymphangiectasia and a chromosomal abnormality. The chromosomal abnormality identified was an isodicentric chromosome 15. Isodicentric chromosome 15 syndrome is characterized by hypotonia, moderate to profound developmental delay and intellectual disability and epilepsy.[7] We are not aware of an association between this disorder and chylothorax. Thus, any contribution of this genetic abnormality to the CC remains uncertain.

Congenital pulmonary lymphangiectasia frequently presents with non-immune hydrops and chylothorax.[6] Open lung biopsy is the 'gold standard' for diagnosis. However, the procedure is invasive and as it was unlikely to alter the clinical management of the patient, was declined. The diagnosis of congenital pulmonary lymphangiectasia was suspected in our patient based on clinical and radiologic characteristics. Chest radiographs and CT imaging demonstrated mild, diffuse, unilateral pulmonary interstitial thickening. Though the degree of interstitial thickening was described as mild, chest CT findings in pulmonary lymphagiectasia are herterogeneous with a spectrum of severity.[8] Medical management options for chylothorax are limited primarily to restricting the intake of chyle-generating long-chain fatty acids or using parenteral nutrition, and, occasionly, octreotide.[2]

Most CC result from malformation of the lymphatic system.[1,2] Recently, case reports have described the successful use of propranolol,[9,10] sirolimus[11] and sildenafil[3] for the management of various lymphatic malformations in infants and children. Of these, sildenafil has been further evaluated in an open label trial for the treatment of children with lymphatic malformations.[3] The trial was conducted after a serendipitous observation in a child with an intrathoracic lymphatic malformation and idiopathic pulmonary hypertension.[4] The pulmonary hypertension was treated with sildenafil and during the course of treatment the lymphatic malformation reduced in size, then enlarged with discontinuation of sildenafil.

A mechanism by which sildenafil may facilitate resolution of CC and lymphatic malformations involves generation of new lymphatic vessels. Physiologic lymphangiogenesis occurs in response to acute and chronic inflammation, serving to reduce inflammation through enhanced clearance of extravasated lymph.[12,13] Lymphatic vessel growth and function is regulated, in part, by nitric oxide-induced production of cyclic guanosine monphosphate. Cyclic guanosine monphosphate mediates lymphatic endothelial cell proliferation, migration and tube formation.[14] Sildenafil prevents the degradation of cyclic guanosine monphosphate by selective inhibition of phosphodiesterase-5 (ref. 15) and could thereby facilitate lymphatic vessel growth and/or remodeling allowing resolution of lymphatic obstruction and chylothorax. Further study in animal models is necessary to determine the mechanism by which sildenafil resolves lymphatic malformations and chylothorax.

It cannot be determined whether the clinical course would have been significantly different had treatment with supportive care and octreotide alone been continued. However, the infant did show prompt resolution of the chylothorax and respiratory symptoms, with no adverse short-term complications, following

initiation of sildenafil. Studies of infants with chylothorax and confirmed pulmonary lymphangiectasia are necessary to determine the efficacy of sildenafil in the management of these conditions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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