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Case Series

Persistent Pulmonary Hypertension in Newborns: A Rare and Perplexing Diagnosis

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Keywords

- Alveolar Capillary Dysplasia
- Misalignment of the Pulmonary Veins

Abstract

Backgrounds: Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) is a rare fatal disease. There are around 200 cases reported in the literature. It is a disorder of immature lobular development and reduced capillary density in the lungs. The pulmonary veins run alongside pulmonary arteries, instead of in the interlobular septa. Mortality to date is nearly 100%

Case Report: We performed a retrospective chart review of five cases of ACD/MPV at our center from 2005-2019. We reviewed clinical history, course of hospitalization, echocardiograms, chest imaging including chest CT, histology including autopsy findings, and the medical management. We present five cases from our center. The diagnosis was confirmed by either autopsy or biopsy. All the newborns had severe PPHN refractory to treatment.

Conclusion: ACD/MPV should always be considered as a cause of severe persistent pulmonary hypertension refractory to treatment including inhaled nitric oxide, conventional mechanical ventilation, and medical management. It is imperative to have a high index of suspicion in cases of severe refractory pulmonary hypertension and confirm the diagnosis of ACD/MPV as early as possible. Developing and implementing an institutional algorithm for the management of these cases can help to ensure that everyone involved in care of the patient are considering at the big picture including utilization of resources while combating with some very practical challenges.

INTRODUCTION

In 1981, Janney et al. "observed a case of an infant in which the ingrowth of capillaries, and formation of blood air barriers at capillary-epithelial interface, apparently failed to take place." The infant was born at term with a clinical course consistent with the syndrome of persistent fetal circulation. She died at 40 hours of age. This was the first report in the literature of a case of alveolar capillary dysplasia, one of the most unusual causes of persistent pulmonary hypertension of the neonate (PPHN) [1].

Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) is a rare fatal disease. There are around 200 cases reported in the literature. It is a disorder of immature lobular development and reduced capillary density in the lungs. The pulmonary veins run alongside pulmonary arteries, instead of in the interlobular septa. Mortality to date is nearly 100%.

In 95% of cases, ACD/MPV patients are born full term with normal birth weights and Apgar scores [2,3]. We present five cases from our center. The diagnosis was confirmed by either autopsy or biopsy. All the newborns had severe PPHN refractory to treatment.

METHODS

The Institutional Review Board at Nationwide Children's Hospital determined this study not to be human subject research and informed consent was not required

We performed a retrospective chart review of five ACD/MPV cases at our center from 2005-2019. We reviewed clinical history, course of hospitalization, echocardiograms, chest imaging including chest CT, histology including autopsy findings, and medical management.

CASE REPORTS

Case 1

A male neonate born at 39 weeks gestational age (GA) with Apgar scores 8 and 9 at 1 and 5 minutes respectively. At 10 hours of age, he developed respiratory distress secondary to bilateral pneumothoraxes treated with thoracentesis. Echocardiogram (ECHO) revealed a large patent ductus arteriosus, patent foramen ovale, right ventricle enlargement, and estimated RVSP of 56mmHg plus right atrial pressure indicative of PPHN. He developed respiratory failure on day two of life and was not responsive to conventional mechanically ventilation and high

frequency oscillatory ventilation. Patient was therefore initiated on ECMO and Treprostinil on day 13 of life. Evaluations of possible causes of interstitial lung disease including surfactant deficiency disorders were pursued. Considering the dismal prognosis, life support was withdrawn at parental request. The patient survived for 20 days.

Autopsy of the lung revealed abnormal lobular development and deficient capillary vascularity. The diagnosis of ACD/MPV was made with lack of capillaries in alveolar space, presence of intravascular thrombi, and patchy acute pneumonia (Figure 1). The diagnosis was further confirmed by genetic testing which was positive for FOXF1.

Case 2

A male neonate born at 38 weeks with Apgar scores 7 at 1 minute and 8 at 5 minutes. Around 12 hours of life, he developed severe respiratory failure. Imaging revealed bilateral pneumothoraxes which were treated with multiple thoracentesis. ECHO demonstrated PPHN and treatment included mechanical ventilation, inhaled nitric oxide (iNO) and ECMO.

Wedge open biopsy of right lower lobe of the lung was performed on day 22 of life which showed ACD/MPV (patchy intra-alveolar neutrophilic exudate and simplification of alveolar architecture, decreased alveolar capillaries, lymphangiectasis, and small pulmonary veins course along small pulmonary arteries -misalignment of veins). The elastic stain shows prominent medial thickening of small arteries and muscularization of arterioles. Given the unfavorable prognosis, life support was withdrawn at three months of age.

Case 3

A female neonate was born at 40 weeks GA, Apgar scores of 1 at 1 minute and 6 at 5 minutes and soon developed severe respiratory failure. ECHO was consistent with PPHN. Treatment included mechanical ventilation, iNO, corticosteroids, and vasopressors. The hospital course was complicated with bilateral pneumothoraxes requiring thoracentesis. Patient survived for 12 days of life. Autopsy revealed ACD/MPV, associated with decrease in small veins of the interlobular septae. Maldevelopment of the acini, with decreased volume and simplification of structure, and constricted small arterioles were also identified.

Case 4

A male neonate born at 37 weeks gestational age, Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. He developed respiratory distress soon after birth requiring mechanical ventilation. ECHO revealed PPHN. Treatment included mechanical ventilation and iNO and eventually placed on VA-ECMO.

Lung biopsy was performed on day 14 of life which was diagnostic of ACD/MPV; enlarged alveolar space with thickened septate, scattered arterioles and capillaries. Due to the poor prognosis and careful consideration of ethical dilemmas by the medical team and family, the parents decided to withdraw support. Patient survived for 16 days.

Case 5

A female neonate born at 38 weeks gestational age, developed respiratory failure and PPHN at birth. Treatment included failed mechanical ventilation, surfactant, iNO for five days followed by ECMO. Lung biopsy on day seven showed ACD/MPV. She underwent combined heart-lung transplant at the age of 17 days of life. She developed cardiorespiratory failure at 40 days of life. Given the poor prognosis of the disease and lack of options for further treatment, the parents requested withdrawal of life support. The patient survived for 40 days.

DISCUSSION

We found that 60% of the patients were males. All the patients were full term and developed respiratory distress followed by respiratory failure soon after birth. ECMO was started in 80% within the first few days of life. Biopsy proven findings of ACD/MPV was reported in 60% of cases. Diagnosis was confirmed upon autopsy in 40% of cases. Due to the dismal prognosis, 80% of the patients had withdrawal of care. Death due to the severity of illness was documented in 33% of cases. Only two had chest CT. The FOXF1 was positive in both these patients. Mean age of survival was 32.6 days with longest survival of 90 days.

ACD/MPV presents in the neonatal period with minimal or no parenchymal lung disease and is fatal. Severe PPHN crisis and right ventricular failure are nearly always present. To date, there are no reports of computed tomography or magnetic resonance lung imaging in infants with a confirmed diagnosis of ACD/MPV. The current gold standard to unambiguously diagnose ACD/MPV is histological examination of the lungs. In majority of the studies, most cases were diagnosed by autopsy [2-4], and 65% of the cases were associated with other congenital abnormalities. Recently the FOXF1 gene has been found to be associated with ACD/MPV in 40% of cases examined.

Reported mortality to date is almost 100%. The only treatment option is lung transplantation. Due to the nature of the disease, patients will need to be listed for transplant shortly after the diagnosis made. Obtaining lung transplantation can take days to years. In addition, there is a scarcity of donors in this specific age group. As to the issue of donor availability, each year there are approximately 100 cadaveric donors under the age of 1 year. For other age groups, 15% of organ donors will have lungs suitable for transplantation [5]. If the same figures apply, 15 donors for infant recipients should be available annually in the United States [5].

Bridging with ECMO till organs can be available for transplantation is part of the therapeutic plan. Several studies have shown that ECMO, has side effects, and it has a negative effect specifically on neonates. Some of the side effects include central nervous system dysfunction and severe pulmonary dysfunction [6]. The longest duration of ECMO support mentioned in the pediatric literature is 48 days [7,8]. It is known that the survival rate is low, and complications are high. As in other studies, the most common complications in this study were related to bleeding, thromboembolic events, and nosocomial infections [9-12]. In fact, prolonged ECMO use is known to increase the chance

of nosocomial infection, which in turn is known to increase the duration of ECMO [13, 14].

ECMO is typically initiated in a time sensitive manner; leaving the medical team with minimal time for a lenghty discussion with the neonate's family about the ECMO support goals and duration of support. Early clarification about the expectations, the discontinuation strategy plans, and the acceptable functional outcomes following ECMO separation is of the utmost need. A multidisciplinary team-based approach and institutional algorithm is required to aid in making the decision making a well-planned and ethically appropriate for the medical team and family. This includes involving the palliative and ethics team as part of treatment algorithm [15,16]. While the patient is on ECMO support, the family should be informed with frequent updates about the results of outcomes of ECMO support for the patient.

In order to initiate the therapeutic plan including bridge ECMO and placing on the transplant list, the diagnosis should be confirmed by lung biopsy and supplementary FOXF-1 genetic testing. This is will be the first step in the algorithm for management of neonates with severe refractory pulmonary hypertension. Once the diagnosis has been established, careful discussion with the family and the multidisciplinary team, the patient can be considered to be placed on ECMO or undergo withdrawal of life support. Autopsy should be considered and encouraged in the management algorithm for patients who died before undergoing a lung biopsy. This will aid in genetic counselling for the parents interested in the same.

CONCLUSION

It is imperative to have a high index of suspicion in cases of severe refractory pulmonary hypertension and confirm the diagnosis of ACD/MPV as early as possible. Developing and implementing an institutional algorithm for the management of these cases can help to ensure that everyone involved in care of the patient are considering at the big picture including utilization of resources while combating with some very practical challenges.

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