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Comprehensive management for the improved outcome of persistent pulmonary hypertension of the newborn in a one-day-old baby girl: a case report



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ABSTRACT

Introduction: Persistent pulmonary hypertension of the newborn (PPHN) is characterized by an increase in pulmonary vascular resistance (PVR), caused by failure of circulatory adaptation within minutes after delivery. Persistent pulmonary hypertension of the newborn (PPHN) can lead to severe respiratory distress and hypoxemia. Newborns with PPHN are at high risk of severe asphyxia and its complications. This study aims to present a comprehensive assessment and treatment of newborn PPHN that might be applicable in any hospital setting.

Case description: A one-day-old baby girl came to the emergency room with the chief complaint of cyanosis since birth. The baby was born with oxygen, with pre-ductal and post-ductal differentiation of 5%. The baby showed weak crying movements and inadequate spontaneous breathing, indicating persistent respiratory distress and a chest x-ray revealed pneumonia. The echocardiogram showed a bidirectional secundum, an atrial septal defect, moderate patent ductus arteriosus, and severe pulmonary hypertension. Sputum culture showed *Klebsiella pneumoniae* (ESBL). Comprehensive management was given to the patient. After several days of hospitalization, the patient was discharged in good condition.

Conclusion: PPHN is associated with high morbidity and mortality in newborns. Comprehensive evaluation and management of PPHN and control of any comorbid conditions must be performed to improve patient outcomes.

Keywords: cyanosis, newborn, pulmonary arterial hypertension.

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INTRODUCTION

Persistent pulmonary hypertension in the newborn is characterized by a sustained increase in pulmonary vascular resistance that results from failure of the normal circulatory adaptation to extrauterine life. This causes right-to-left blood flow through the foramen ovale and ductus arteriosus and inhibits pulmonary blood flow increment, which is important for extrauterine oxygenation and survival.^{1,2}

The incidence of PPHN is recorded at 2/1,000 live births, being the highest in term and late preterm infants.³ Despite advances in neonatal cardiorespiratory care, PPHN is still a major cause of neonatal morbidity and mortality, with a mortality rate of 4–33%. PPHN is associated with several etiological possibilities related to severe outcomes. Up to 25% of infants with PPHN will have significant neurodevelopmental

impairment at 2 years of age.^{4,5}

Although this condition is considered life-threatening, in most cases, PPHN is reversible in the first days of life, if the etiology-related conditions have been improved.^{3,6} However, the heterogeneity of etiopathogenic factors can hinder standardized management, thus creating challenges in diagnosis and management.^{1,7}

It is intended that a better understanding of PPHN may help in the process of making a diagnosis and providing more effective treatment.⁸ The patient, in this case, was worsened by pneumonia due to an ESBL (extended-spectrum beta-lactamases) infection, which made the treatment more challenging and required comprehensive management than other cases of PPHN in newborn babies. We performed comprehensive assessment and treatment that might be applicable in any hospital setting.

CASE DESCRIPTION

A one-day-old baby girl was referred to the emergency room with the chief complaint of cyanosis that had occurred since birth. The patient was born at 38 weeks with a birth weight of 3200 grams, delivered by cesarean section due to premature rupture of membrane (PROM) > 12 hours. The patient had cyanosis. Her right arm (pre-ductal) saturation was 89%, and her left leg (post-ductal) saturation was 84%. The difference between pre-and post-ductal saturation was five, indicating there was a cardiac problem in this patient. The APGAR score was 3 at 1 minute and 5 at 5 minutes. The patient was given oxygen supplementation using O2 CPAP (PEEP 7 cmH2O FiO2 30%) in the previous hospital and was suspected of having critical cyanotic heart disease.

The patient also had respiratory distress with a Downe score of 3–4 with substernal

retraction. There was a history of fever, respiratory distress, and leukocytosis, which aligns with chest radiography showing pneumonia. Empirical antibiotics were administered using ampicillin-sulbactam and gentamicin. Continuous positive airway pressure (CPAP) was put on her in the neonatology ward, and the saturation reached 100%.

According to the patient's condition, an echocardiography examination was performed. We found a bidirectional secundum atrial septal defect, moderate patent ductus arteriosus, and moderate tricuspid regurgitation, with the conclusion of severe pulmonary hypertension. Therefore, sildenafil was given with a gradual titration starting at 0.7 mg/kg/dose Q8H on the first day in the perinatology ward. Partial parenteral nutrition was given using glucose infusion rate (GIR)^{3,5}, and breast milk as enteral feeding.

On the third day of hospitalization, the respiratory distress worsened. The fever persisted, and procalcitonin increased, indicating a septic condition. Blood gas analysis showed respiratory failure; the patient was transferred to the NICU using an NIV. The sputum culture was performed and showed *Klebsiella pneumoniae* (ESBL), which was sensitive to cefoperazone sulbactam. The antibiotic was escalated from ampicillin sulbactam to cefoperazone sulbactam.

On the eighth day of hospitalization, respiratory distress was sustained. The patient was intubated and put on mechanical ventilation, with oxygen saturation optimized until 100%. The antibiotic was switched according to the sputum culture. Fentanyl was added as an analgesic and sedative. Sildenafil was titrated to 3x3mg (0.8 mg/kg/times).

In the second week of treatment, the patient started to show improvement in their condition. The patient suffered from a septic condition during the second week of hospitalization. Sildenafil was titrated until 3x5 mg (1.5 mg/kg/time).

On the third week of treatment in the NICU, a chest X-ray evaluation was done and showed lung infiltrates had decreased. The patient was extubated and weaned into room-air oxygenation. She was transferred to the regular perinatology ward.

Echocardiography evaluation on the 29th day of hospitalization showed significant improvement in pulmonary hypertension; tricuspid regurgitation improved from moderate to mild; and the PDA closed spontaneously. The patient was extubated and weaned to room air. She was then transferred to the regular perinatology ward. The patient was discharged from the hospital after 32 days of hospitalization and sent to the outpatient clinic.

DISCUSSION

The pathogenesis of PPHN is multifactorial, also involving several perinatal risk factors such as maternal exposures. Persistent pulmonary hypertension in newborns is often secondary to parenchymal lung disease (such as meconium aspiration syndrome, pneumonia, or respiratory distress syndrome) or lung hypoplasia (with congenital diaphragmatic hernia or oligohydramnios), but can also be idiopathic.^{3,6} PPHN may be idiopathic (10%) or secondary to certain neonatal pulmonary diseases, which lead to delayed relaxation of the pulmonary vascular bed. In this case, risk factors for PPHN were delivered through cesarean section, early term newborn, and aggravated by pneumonia. Pneumonia was the risk factor for the patient's development of respiratory distress and sepsis. Pneumonia leads to failure of the pulmonary circulation to undergo the normal transition after birth, leading to PPHN in this case.

The patient was presented with a history of cyanosis, and the difference between pre-ductal and post-ductal oxygen saturation was five percent. In a hypoxemic neonate, differentiating cyanotic congenital heart disease from PPHN is important. The initial evaluation should include a thorough history and physical examination, simultaneous measurement of preductal and postductal oxygen saturation, a hyperoxia test, chest radiography, and early echocardiography.

Hypoxemia disproportionate to the severity of parenchymal disease on chest radiography should suggest idiopathic PPHN (or cyanotic heart disease). Pre-ductal and post-ductal oxygen saturation and PaO₂ measurements are used to differentiate PPHN from structural heart disease.^{9,10} A saturation difference of greater than 5% to 10% or a PaO₂

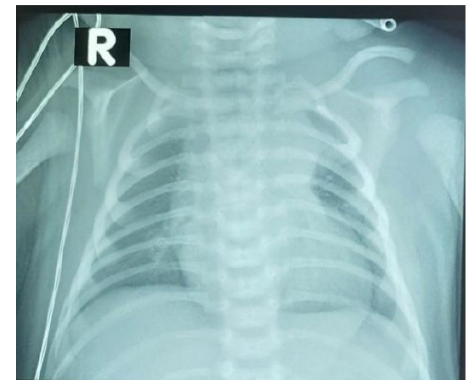


Figure 1. Chest radiography at first admitted in ER showing Pneumonia and there was no LVH nor RVH.



Figure 2. (A) Chest radiography at first admitted in ER showing Pneumonia and there was no LVH nor RVH. (B) The patient was transferred to the Perinatology Ward and his oxygen saturation reached 100% with O₂ CPAP PEEP 7cmH₂O FiO₂ 30%.



Figure 3. On the 8th day of hospitalization, the patient was transferred to NICU and intubated due to increased respiratory distress. The picture showed oxygen saturation reached 100% with O₂ ETT PCV PEEP mode 7 cmH₂O PIP 16 cmH₂O RR 40x/minute Ti 0.5 s FiO₂ 50%.

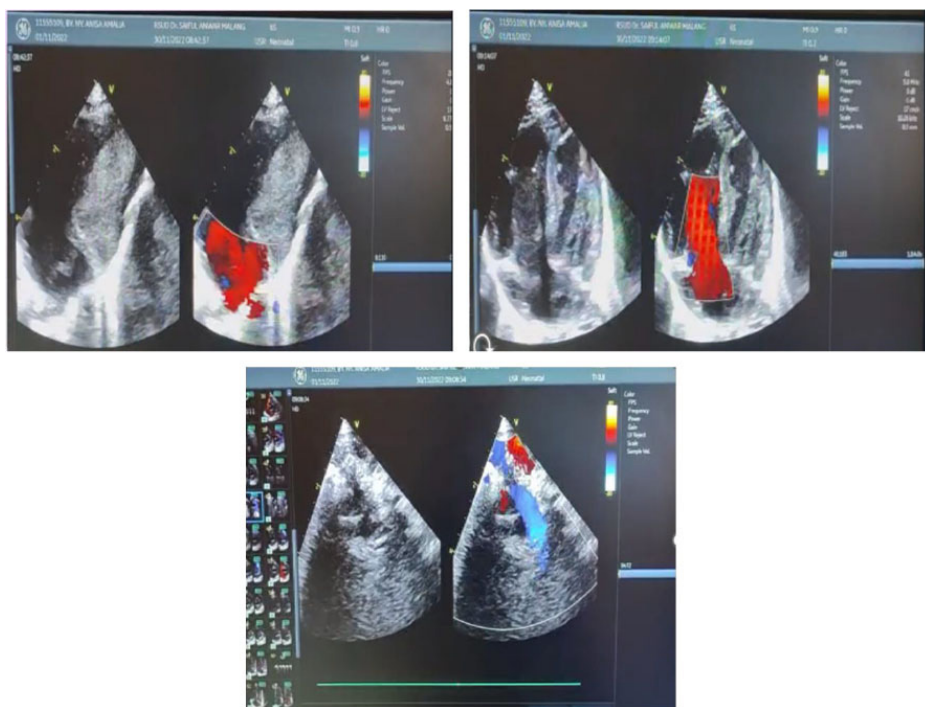


Figure 4. Echocardiography of this patient showed a bidirectional secundum ASD, moderate fetal PDA, and TR moderate with severe pulmonary hypertension.

difference of 10 to 20 mm Hg between the right upper and lower legs was considered significant. In a neonate with PPHN and a right-to-left atrial-level shunt.^{7,11}

In a patient with cyanosis at birth, but after a hyperoxia test with 100% oxygen or positive pressure, the saturation could reach 100%, the diagnosis of cyanotic CCHD (Critical Congenital Heart Defects) could be ruled out. An echocardiogram confirmed the diagnosis of PPHN, and comprehensive treatments should be administered. From the echocardiogram, we found bidirectional secundum ASD, moderate fetal PDA, and moderate TR, concluding severe pulmonary hypertension.

Providing adequate oxygenation is crucial for PPHN management. Hypoxia increases pulmonary vascular resistance and contributes to the pathophysiology of PPHN. After the oxygenation management, the patient was arranged to have 100% saturation from the first day of hospitalization. The patient saturation could reach 100% after being given CPAP. On the second week of hospitalization, the patient was intubated and put on mechanical ventilation for several days. Monitoring of oxygen therapy in PPHN could be done via invasive and noninvasive methods. Non-invasive pulse oximetry measures peripheral saturations (SpO₂), and a target range of 91–95% is recommended during acute PPHN management.¹² Maintaining pre-ductal oxygen saturation in the low to mid-90s with a PaO₂ between 55 and 80 mm Hg during the management of infants with PPHN is preferable. Oxygen is a specific and potent pulmonary vasodilator, but it can increase oxidative stress if used in excess.¹³ In this case, blood gas analysis was taken several times during the therapy to monitor oxygenation.

Pneumonia, as one of the leading factors in PPHN in this patient, was also treated aggressively. Empirical antibiotics, ampicillin-sulbactam and gentamicin, were given at the time of admission. Respiratory distress and the evaluation of chest radiography had not improved. Procalcitonin was increased, and marked sepsis is still ongoing. A blood culture was taken, which resulted in *Klebsiella pneumoniae* (ESBL). The antibiotic

was switched according to the sputum culture result, which was *Klebsiella pneumoniae* and sensitive to cefoperazone sulbactam. The complete blood count and procalcitonin were improved and able to be extubated.

Because of pulmonary vasoconstriction is also triggered by low basal production of vasodilators such as prostacyclin and nitric oxide (NO).⁵ The patient in this case was treated with Sildenafil 2.5 mg (gradual titration) three times daily. Sildenafil has been studied and used for the treatment of pulmonary hypertension in adults and neonates. Sildenafil, a phosphodiesterase-V inhibitor, is a first-line treatment choice. PDE-5 is found at high levels in the pulmonary circulation.¹⁴ Its administration should be under the careful observation of a pediatric cardiologist. A high risk of hypotension was observed during IV administration. In this case, sildenafil was given by oral administration and titrated gradually with close observation of blood pressure and vital signs.

We added fentanyl to this patient for sedation and analgesia to minimize pain. Use of sedation and analgesia with narcotic analgesics like fentanyl and morphine or benzodiazepines such as midazolam is also recommended to provide a rapid analgesic effect and minimize stimulus.^{13,15} Due to underlying shunts, any stimulus can result in a precipitous drop in oxygen saturation.¹⁴ Paralysis should also be avoided, as it has been associated with increased mortality.¹⁵

In newborns with severe pulmonary disease, as in this patient, high-frequency ventilation is often used to optimize lung inflation and minimize lung injury. Optimal lung expansion (expansion of 8 to 9 ribs on an inspiratory chest radiograph) using positive end-expiratory pressure (PEEP) or mean airway pressure is proven to reduce PVR. Both under-inflation and over-inflation of the lungs will cause an increase in PVR. A gentle ventilation strategy with optimal PEEP, relatively low peak inflation pressures or tidal volumes, and a degree of permissive hypercapnia is recommended to ensure adequate lung expansion while limiting barotrauma and volutrauma.¹⁷

In this case, the patient was given optimal treatment according to the assessment that might be applicable in any hospital setting. However, it cannot be denied that a nosocomial infection might worsen the PPHN condition. This needs to be a concern for patients during the treatment period, especially for patients with PPHN who are treated in hospitals with quite high rates of antibiotic resistance.

CONCLUSION

Healthcare providers should be aware of the need to diagnose PPHN in newborns due to its high morbidity and mortality. In addition to the standard examination done after birth, they may perform the following tests on patients with hypoxemia: Pulse oximetry and hyperoxia tests measure blood oxygen levels in a non-invasive way. A chest x-ray and echocardiogram should be done to diagnose PPHN. As soon as PPHN is diagnosed, comprehensive patient management is necessary for an improved outcome. Identifying and treating the etiologies of PPHN are also important. Sildenafil has beneficial effects in PPHN therapy and should be given with close monitoring of the patient's hemodynamic and vital signs.

DISCLOSURES

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Conflict of Interest

None.

Ethical Statement

The patient has given informed consent regarding the publication of this case.

Author Contribution

All authors contributed to manuscript preparation and agreed this final version of the manuscript to be submitted.

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