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Severe Neonatal Cardiopulmonary Failure with Suspected RASopathy: A Case Report

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Abstract: ***Neonatal cardiopulmonary failure may reflect underlying genetic disorders, including RASopathies caused by dysregulation of the RAS–MAPK signaling pathway. We report a late preterm neonate with severe cardiopulmonary compromise in whom whole-exome sequencing identified a heterozygous RAF1 missense variant (c.991A>T; p.Arg331Trp), along with a ZIC3 variant. The RAF1 variant has not been previously described and may represent an expanded phenotypic spectrum of RAF1-associated disease. This case underscores the challenges of interpreting novel genomic variants in critically ill neonates and highlights the importance of correlating molecular findings with clinical presentation. Reporting such rare variants is essential to refine genotype–phenotype relationships and improve diagnostic accuracy in neonatal RASopathies.***

Keywords: Neonate, PAH, genetic, cardiomegaly, PDA, coagulopathy

1. Introduction

Neonatal cardiopulmonary failure represents a critical presentation in the early neonatal period and is commonly associated with conditions such as persistent pulmonary hypertension of the newborn (PPHN), congenital heart disease, sepsis, and metabolic disorders.[1] Advances in genomic medicine have highlighted the role of underlying genetic conditions in severe and atypical neonatal presentations. RASopathies are a group of genetic disorders involving the RAS–MAPK signaling pathway and may contribute to complex cardiac and multisystem involvement.[2,3] Interpretation becomes challenging when variants of uncertain significance are identified in critically ill neonates.[4] We report a late preterm neonate who presented with severe cardiopulmonary failure, refractory metabolic acidosis, persistent coagulopathy, and a hemodynamically significant patent ductus arteriosus, with whole-exome sequencing revealing a RAF1 variant of uncertain significance, highlighting the diagnostic complexity and clinical challenges in such cases.[5]

2. Case Report

A late preterm female neonate (36 + 5 weeks) was born by cesarean section to a primigravida mother with no history of consanguinity and no clinical syndromic features. Antenatal scans were unremarkable. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The baby maintained stable vital signs at birth, initiated breastfeeding, tolerated feeds well, and was discharged on day 2 of life.

On day 4 of life, the neonate presented to the emergency department with grunting, mottling, cyanosis, poor respiratory effort, and inability to maintain oxygen saturation. She was immediately transferred to the neonatal intensive care unit and intubated due to worsening respiratory distress. As she failed conventional mechanical ventilation, high-frequency oscillatory ventilation (HFOV) was initiated. Arterial blood gas analysis revealed severe metabolic acidosis (pH 6.84, bicarbonate 7.8 mmol/L, base excess −25), for which normal saline boluses and bicarbonate correction were administered. Chest radiography showed cardiomegaly with bilateral diffuse pulmonary infiltrates. Inotropic support was initiated for hemodynamic instability, and central venous access was established.

Two-dimensional echocardiography demonstrated a large hemodynamically significant patent ductus arteriosus (4.8 mm) with left-to-right shunt and severe pulmonary arterial hypertension. Intravenous paracetamol was started for PDA management, along with milrinone, iNO and multiple inotropes for pulmonary hypertension. Laboratory evaluation revealed coagulopathy, necessitating repeated fresh frozen plasma transfusions. Despite supportive care, the infant exhibited persistent coagulopathy with hypofibrinogenemia, elevated ferritin (6840 ng/mL), progressive pulmonary hypertension, cardiomegaly, neonatal cholestasis, and recurrent pulmonary hemorrhage. Serial echocardiograms showed worsening pulmonary pressures (35 + RAP initially, progressing to 75 + RAP and later 100 + RAP) despite iNO, sildenafil and milrinone. In view of suspected inborn error of metabolism, whole-exome sequencing was performed and identified heterozygous missense variants in RAF1 (c.991A>T; p. Arg331Trp) and ZIC3, both classified as variants of uncertain significance. Despite maximal supportive care, the infant succumbed on day 14 of life.

3. Discussion

Our case illustrates the diagnostic complexity of severe neonatal cardiopulmonary failure in the setting of a RAF1 variant of uncertain significance. The infant presented with refractory pulmonary hypertension, metabolic acidosis, persistent coagulopathy, and a large hemodynamically significant patent ductus arteriosus, leading to progressive respiratory compromise. Although early neonatal presentation without classic Noonan dysmorphic features is uncommon, genetic etiologies should be considered in atypical and severe clinical courses.

RASopathies, particularly those involving RAF1, are increasingly recognized as contributors to critical cardiopulmonary presentations ranging from lethal neonatal pulmonary hypertension and hypertrophic cardiomyopathy to variable cardiac manifestations in older children, including arrhythmias and structural defects, with occasional multisystem involvement such as cerebral hemorrhage.[6-9]

In our patient, whole-exome sequencing identified a heterozygous RAF1 missense variant (c.991A>T; p.Arg331Trp), which has not been previously reported and is currently classified as a variant of uncertain significance. Given the severity of cardiopulmonary failure, persistent pulmonary hypertension, coagulopathy, and multiorgan involvement, this novel variant may represent an expanded or previously unrecognized phenotype. While causality cannot be definitively established, continued reporting and longitudinal surveillance of similar variants are essential to refine genotype–phenotype correlations and improve diagnostic clarity. This case contributes to the evolving understanding of RAF1-associated neonatal disease and underscores the importance of documenting novel variants in critically ill neonates.[10]

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