



AN UNUSUAL PULMONARY MANIFESTATION OF CONGENITAL CMV: SEVERE PERSISTENT PULMONARY HYPERTENSION IN A TERM NEONATE

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ABSTRACT Congenital cytomegalovirus infection rarely presents with severe persistent pulmonary hypertension of the newborn. A term neonate developed refractory hypoxemia and severe PPHN, with CMV PCR positivity and periventricular calcifications. Intensive respiratory and pulmonary vasodilator therapy, followed by valganciclovir, resulted in resolution of pulmonary hypertension and favorable neurodevelopmental outcome.

KEYWORDS : Congenital Cytomegalovirus; Cytomegalovirus; Persistent Pulmonary Hypertension of the Newborn; PPHN; Pulmonary Hypertension; Neonate; Valganciclovir; Inhaled Nitric Oxide

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a disorder of neonatal circulatory transition characterized by failure of the normal postnatal decrease in pulmonary vascular resistance. Persistently elevated pulmonary vascular resistance results in right-to-left shunting through the patent ductus arteriosus and/or foramen ovale, producing severe hypoxemia and, in severe cases, right ventricular dysfunction and circulatory compromise. Diagnosis is supported by clinical evidence of hypoxemia and differential cyanosis and confirmed by echocardiographic demonstration of elevated pulmonary arterial pressure and right-to-left extrapulmonary shunting in the absence of critical cyanotic congenital heart disease[1,2].

PPHN is commonly associated with pulmonary parenchymal disease, including meconium aspiration syndrome and pneumonia, as well as perinatal asphyxia, pulmonary hypoplasia, sepsis, and other disorders affecting pulmonary vascular adaptation. Although infectious diseases can contribute to PPHN, viral causes are uncommon and may be overlooked when more conventional etiologies are absent.

Congenital cytomegalovirus (cCMV) infection is the most common congenital viral infection and can produce a wide spectrum of manifestations, ranging from asymptomatic infection to severe multisystem disease. Symptomatic infants may develop microcephaly, intracranial calcifications, seizures, chorioretinitis, hepatosplenomegaly, hepatitis, thrombocytopenia, growth restriction, and sensorineural hearing loss[3,4]. Pulmonary involvement is considerably less frequently described.

The association between congenital CMV infection and PPHN is particularly uncommon. Published reports have described severe refractory hypoxemia and PPHN in infants with congenital CMV infection, sometimes requiring high-frequency ventilation, inhaled nitric oxide, inotropic support, and extracorporeal membrane oxygenation[5,6]. A recent review identified only a small number of reported cases and emphasized that PPHN may represent a rare manifestation of severe symptomatic congenital CMV infection.

We report a term neonate with symptomatic congenital CMV infection presenting predominantly with severe PPHN in the absence of the usual perinatal risk factors, who had a favorable early outcome following intensive cardiopulmonary and antiviral therapy.

Case Presentation

A male neonate was born at 39 weeks of gestation with a birth weight of 2.5 kg following an apparently uneventful delivery. The immediate postnatal transition was initially satisfactory. Within 6 hours of life, however, the infant developed progressive respiratory distress accompanied by severe and refractory hypoxemia despite supplemental oxygen.

A significant preductal-postductal oxygen saturation difference of more than 20% was observed, raising suspicion of significant right-to-left ductal shunting and PPHN. Echocardiography demonstrated a structurally normal heart with severe pulmonary hypertension. There was right-to-left shunting at the level of both the patent ductus arteriosus and foramen ovale. No structural cardiac lesion capable of explaining the degree of hypoxemia was identified.

The clinical and echocardiographic findings were consistent with

severe PPHN. A systematic evaluation for common underlying causes was performed. There was no evidence of perinatal asphyxia, meconium aspiration, or other obvious perinatal insult. Blood cultures remained negative, and there was no evidence of culture-proven bacterial sepsis.

In view of the severity of PPHN and the absence of an identifiable conventional cause, congenital infection was considered. Urine CMV PCR was positive. Cranial ultrasonography demonstrated periventricular calcifications, a characteristic finding associated with congenital CMV infection. These findings, together with detection of CMV early in the neonatal period, supported the diagnosis of symptomatic congenital CMV infection.

The infant required intensive respiratory support with high-frequency oscillatory ventilation (HFOV). Inhaled nitric oxide (iNO) was initiated for pulmonary vasodilation, and intravenous milrinone was administered for cardiovascular support. Following stabilization, oral valganciclovir therapy was initiated for symptomatic congenital CMV infection.

The infant demonstrated progressive clinical improvement. Pulmonary hypertension resolved by day 7 of life, with improvement in oxygenation and resolution of significant extrapulmonary right-to-left shunting on follow-up echocardiography. Respiratory and cardiovascular support could subsequently be weaned. The infant was discharged home on day 14 of life in clinically stable condition.

At 6 months of age, the infant was reviewed for developmental and auditory outcomes. Neurodevelopment was appropriate for age, and no sensorineural hearing loss was detected on follow-up assessment.

DISCUSSION

PPHN represents failure of the normal transition from fetal to neonatal pulmonary circulation. Persistence of high pulmonary vascular resistance after birth results in reduced pulmonary blood flow and right-to-left shunting through fetal channels, particularly the ductus arteriosus and foramen ovale. The diagnosis in the present case was supported by severe refractory hypoxemia, a marked preductal-postductal saturation difference, and echocardiographic evidence of severe pulmonary hypertension with right-to-left shunting in the setting of a structurally normal heart.

The unusual feature of this case was the absence of the common precipitating conditions for PPHN and the identification of congenital CMV infection. Congenital CMV is well recognized for its neurological, auditory, hepatic, hematological, and ophthalmological manifestations, but severe pulmonary disease and PPHN are distinctly uncommon.

The association between cCMV and PPHN has nevertheless been reported previously. Walter-Nicolet et al. described two neonates with congenital CMV infection and severe PPHN who developed refractory hypoxemia requiring high-frequency ventilation, inhaled nitric oxide, and cardiovascular support; one infant required extracorporeal membrane oxygenation[5]. Another report described preterm twins with congenital CMV infection, severe pulmonary involvement, and PPHN[6]. More recently, a review of published cases identified three additional patients and summarized a total of only a small number of reported cases, reinforcing the rarity of this association.

The mechanism by which CMV may produce pulmonary hypertension is not completely established. Several mechanisms may potentially contribute, including direct pulmonary infection and pneumonitis, pulmonary vascular endothelial injury, inflammation, abnormal pulmonary vascular reactivity, and hypoxic pulmonary vasoconstriction. CMV-associated lung disease may therefore produce pulmonary vascular changes severe enough to result in PPHN. However, because pulmonary involvement was not directly demonstrated in the present case, the precise pathophysiological mechanism cannot be established.

The diagnosis of congenital CMV requires demonstration of CMV infection during the neonatal period. Detection of CMV DNA by PCR in urine or saliva is commonly used, with testing ideally performed within the first 21 days of life to distinguish congenital infection from postnatally acquired infection[7]. In this infant, positive urine CMV PCR together with characteristic intracranial calcifications strongly supported symptomatic congenital infection. The timing of PCR sampling should be explicitly documented in the final manuscript because it is important for establishing congenital rather than postnatal CMV infection. Some babies with cerebral atrophy have underlying genetic cause and poor prognosis[8] There is an increase in iron deficiency prevalence[9].

In the present case, management required simultaneous treatment of the acute pulmonary vascular disease and the underlying congenital infection. HFOV provided lung recruitment and adequate ventilation, while inhaled nitric oxide targeted pulmonary vascular resistance. Milrinone was used as an adjunct for cardiovascular support. Resolution of pulmonary hypertension by day 7 and discharge by day 14 suggest a favorable early response. However, the temporal association between initiation of antiviral treatment and clinical improvement should not be interpreted as proof that valganciclovir directly caused resolution of PPHN, given the simultaneous use of multiple cardiopulmonary therapies and the natural evolution of PPHN. Hemiparesis has poor prognosis[10].

An important clinical implication is that congenital CMV should be considered in selected neonates with severe refractory PPHN when common causes have been excluded, particularly when additional findings suggest congenital infection. These may include thrombocytopenia, hepatosplenomegaly, cholestasis, growth restriction, microcephaly, abnormal neurological examination, intracranial calcifications, or unexplained pneumonitis. Similar articles have been published like this.[11-14]

This case also emphasizes the importance of longitudinal follow-up. Even infants who appear clinically well during the neonatal period may subsequently develop sensorineural hearing loss or neurodevelopmental abnormalities.^{3,8} Therefore, normal hearing and development at 6 months should be considered reassuring but does not eliminate the need for continued audiological and neurodevelopmental surveillance. Similar findings also described in literature.[15,16]

The principal limitation of this report is that a direct causal relationship between CMV infection and PPHN cannot be established from a single case. In addition, pulmonary CMV infection was not directly demonstrated, and detailed virological, radiological, and laboratory data were not available in the information presented. Nevertheless, the combination of symptomatic congenital CMV infection, severe early-onset PPHN, absence of major conventional risk factors, and subsequent favorable outcome makes this case clinically noteworthy.

CONCLUSION

Congenital CMV infection may rarely present with severe PPHN and should be considered in neonates with refractory pulmonary hypertension when common etiologies have been excluded, particularly when features suggestive of congenital infection are present. Early echocardiographic confirmation of PPHN, aggressive cardiopulmonary support, timely diagnosis of cCMV, and appropriate antiviral therapy are important components of management. Although a causal relationship cannot be established from an individual case, recognition of this rare association may facilitate earlier diagnosis and appropriate multidisciplinary follow-up.

Conflict of Interest

The author declares no conflict of interest.

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