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Atypical Causes of Severe Pulmonary Hypertension in Infancy

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Introduction

Pulmonary hypertension (PH) is a progressive disease characterized by elevated pulmonary arterial pressure (PAP). It is defined for both adults and children as mean PAP exceeding 20 mmHg and pulmonary vascular resistance of at least 3 Woods Units (WU; indexed to body surface area in children).[1] A more appropriate suggested definition of PH in infants is a ratio of pulmonary artery systolic pressure to the systemic arterial systolic pressure above 0.4.[2] In addition, cardiac catheterization derived mean pulmonary artery pressures to mean systemic arterial pressure ratio >0.75 indicating severe pulmonary hypertension has been associated with worse outcome in children.[1] PH can be life-threatening and often presents within hours after birth. Persistent PH of the newborn (persistent pulmonary hypertension of the newborn [PPHN]) is a common etiology of PH in infants, occurring in 0.4 to 6 per 1000 live births with increasingly higher frequency reported at earlier gestational ages.[1,3,4] However, rare etiologies of pulmonary hypertension can go unrecognized and may present outside the neonatal period.[5] We present 4 atypical cases of severe pulmonary hypertension and review how early recognition informed prognosis and guided timely intervention.

Case Descriptions

Ethical Approval and Informed Consent: The Cedars-Sinai Institutional Review Board approved this study. All participants' parents or guardians provided written informed consent before enrollment in the study.

Case 1

A 5-day-old term infant presented with a heart murmur and tachypnea. An echocardiogram showed severe right heart dilation, tricuspid regurgitation (TR), and severe PH evidenced by bidirectional ductus arteriosus shunting, dilated superior systemic veins, and diastolic flow reversal in the aortic arch. Chest X-ray showed severe cardiomegaly with pulmonary vascular congestion. The patient was confirmed to have a vein of Galen malformation (VOGM) by brain ultrasound and brain MRI. Multiple hospital readmissions were required for medical management of high-output cardiac failure. Uncomplicated endoscopic embolization of the VOGM occurred at 7 months of age with prompt improved cardiac symptoms and pulmonary pressures.

Case 2

A patient born at 27 5/7 weeks due to preterm labor developed poor respiratory effort and hypoxemia. Noninvasive positive pressure ventilation (NIPPV) was followed by intubation and surfactant; however, these supportive therapies resulted in minimal cyanosis improvement. An echocardiogram at 18 hours of life revealed severe PH, large patent ductus arteriosus (PDA), and patent foramen ovale, both with bidirectional shunting, moderate TR, and right heart dilation. A trial of inhaled nitric oxide (iNO) did not demonstrate a reversal of right-to-left ductal shunting. Over the ensuing 5 weeks, he developed progressively worsening hypoxemic respiratory failure. At 6 weeks of life, he acutely decompensated and was nonresponsive to maximum support. The care team discussed with parents that a higher level of care using extracorporeal membrane oxygenation (ECMO) was not feasible because of the infant's small weight and prematurity. The patient passed away a few minutes after he was transitioned to comfort care. An autopsy showed histopathologic changes consistent with alveolar capillary dysplasia (Figure 1), including reduced pulmonary capillary density located remote from the alveolar epithelium, thickened

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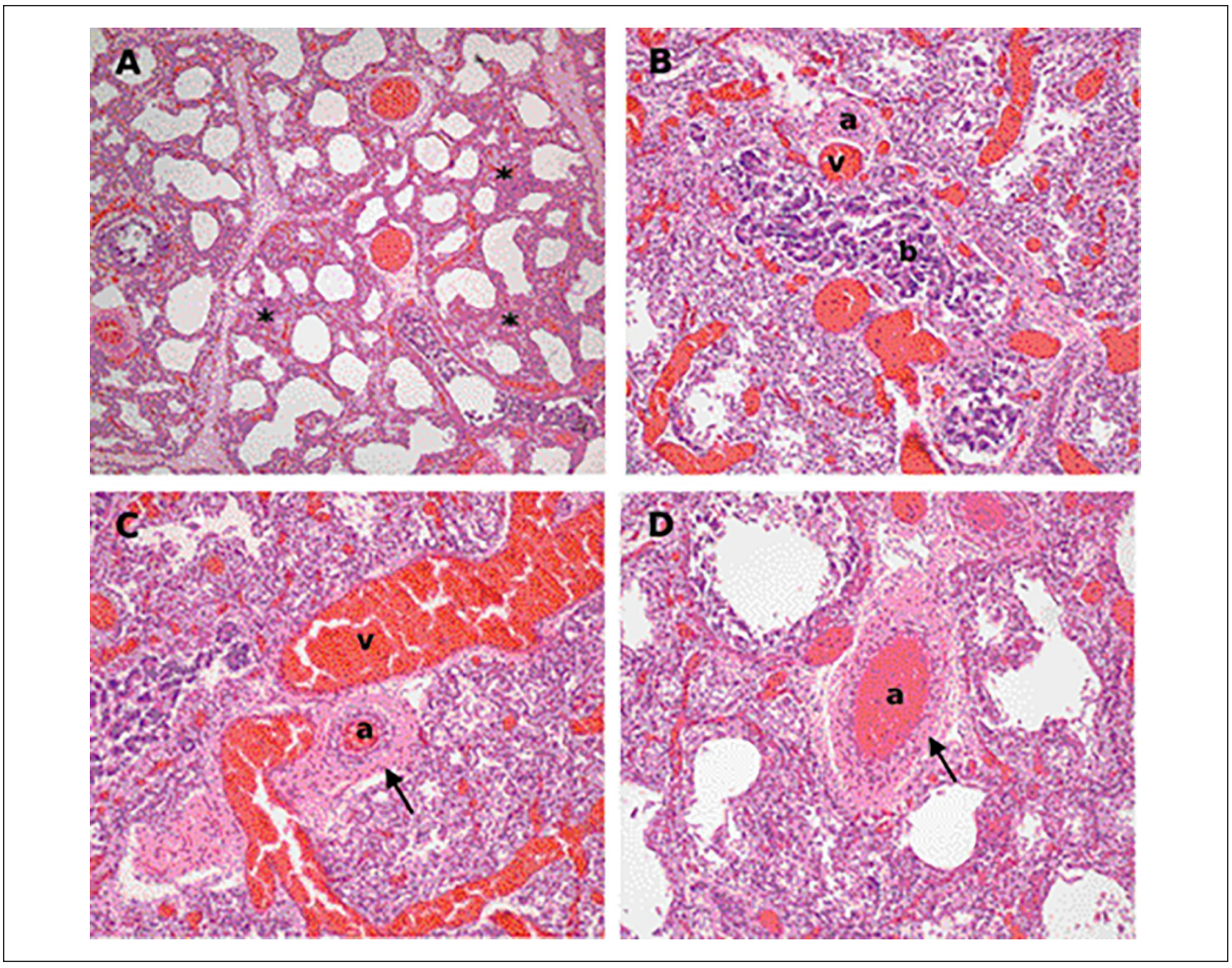

Figure 1. Characteristic congenital alveolar capillary dysplasia findings on histopathology. Formalin-fixed, paraffin-embedded, lung tissues stained with hematoxylin and eosin show the following: (A) Thickened alveolar septae with malpositioned alveolar capillaries (*). (B) Pulmonary venous branches (v) adjacent to pulmonary arteries (a), seemingly within the same vascular sheath. (C) Venous pooling in some foci (v). (D) Medial hypertrophy of small pulmonary arteries with increased muscularization of arterioles (arrows).
a: pulmonary arteries; b: bronchiole; v: pulmonary veins.

alveolar septa, muscularized pulmonary arteries, and dilated bronchial veins.

Case 3

A 37-day-old preterm infant presented with cyanosis and abdominal distension for follow-up of congenital hyperinsulinism (CHI), managed with diazoxide. Rapid response was initiated, and the infant was intubated for impending respiratory failure. Chest X-ray showed cardiomegaly and pulmonary edema. Echocardiography performed on admission showed biatrial and biventricular chamber dilation and mostly right-to-left ductal shunting consistent with suprasystemic PAP. One month prior, a neonatal discharge echocardiogram had demonstrated normal cardiac anatomy and no ductal patency. Management of the severe pulmonary hypertensive crisis included mechanical ventilation, sedation, paralysis, inhaled nitric oxide, aggressive diuresis, and discontinuation of diazoxide. B-type natriuretic peptide of 2252 pg/ml (normal $<$100 pg/ml) from admission improved to 242 pg/ml by hospital day (HD) 5, coinciding with pharmacokinetic time to diazoxide elimination. Transition to oral sildenafil occurred on HD 8 and extubation on HD 18. Diazoxide therapy was resumed at a lower dose with the addition of chlorothiazide on HD 22 due to a lack of other equivalently effective therapeutic options for CHI. Over the next 3 months, there was successful maintenance of normoglycemia on weaning doses of diazoxide and chlorothiazide. Sildenafil was discontinued after serial echocardiograms confirmed the resolution of PH.

Case 4

A 4-month-old term infant with a history of inadequate weight gain presented with cyanosis, poor perfusion, and hypoxemia at the pediatrician's office. In the emergency room, oxygen saturation increased from 60% on presentation to 90% with supplemental oxygen. Chest X-ray showed cardiomegaly. Echocardiography showed a dilated, dysfunctional right ventricle with systolic septal bowing into the left ventricle, estimating suprasystemic PAP. Following PICU admission, NIPPV with iNO and milrinone infusion were initiated. Initial venous blood gas showed a pH of 7.23, PCO2 94, base excess of +12, prompting intubation. Diagnostic catheterization confirmed PH with a pulmonary vascular resistance index at 6.4 WU/m^2 (normal <4 WU/m^2). Upon extubation to NIPPV, he required reintubation for peak PCO_2 of 134 mmHg with regular work of breathing. Chronic carbon dioxide retention was suspected based on the partially compensated metabolic alkalosis (pH 7.03, base excess +13). Whole exome sequencing identified a PHOX 2B 20/25 polyalanine repeat mutation, confirming congenital central hypoventilation syndrome. Tracheostomy and gastrostomy tubes were placed, and an echocardiogram on sildenafil 1 month later demonstrated normal biventricular size, function, and normalized PAP.

Discussion

Typical and atypical etiologies of PH should be considered early in the treatment process, and response to treatment should be assessed concomitantly. This case series highlights atypical etiologies of severe PH in infancy. Features unique to each clinical vignette that reflect the underlying lesions' pathophysiology (Table 1) are described below.

VOGM is a congenital anomaly caused by progressive enlargement of abnormal arteriovenous connections between the choroidal arterial vessels and vein of Markowski during fetal development.[6] The arteriovenous conduit creates an extracardiac left-to-right shunt from the cerebral circulation to the right heart, with consequently progressive high output cardiac failure starting in utero. Severe PH is attributed to the long-standing torrential volume overload through the right heart and pulmonary vasculature, leading to persistently high pulmonary vascular resistance and pressures.[7] Auscultation of a cranial bruit can be appreciated over the anterior fontanelle is VOGM. The shunt characteristically manifests on echocardiography as superior vena caval and right heart dilatation, PH, as well as diastolic flow reversal ("runoff") in the descending aorta. Cranial ultrasound Doppler identifies VOGM in most cases, and brain MRI is used to make a definitive diagnosis. The severity of PH can be mitigated with aggressive anticongestive heart failure therapy, primarily dieresis, and optimal oxygen delivery. Endovascular embolization is required as definitive therapy. However, procedural risks are higher in neonates, and when possible, the procedure is deferred until later in infancy (>5-6 months) to improve outcomes.[8] Progressive hydrocephalus, neurocognitive impairment, or severe PH refractory to medical therapy should prompt earlier treatment. Prognosis depends on the severity of heart failure, neurologic complications, and endovascular procedural success.[8]

Alveolar capillary dysplasia (ACD) is a rare, often fatal, etiology for PH, though some recent studies report a delayed phenotypic presentation with prolonged survival.[9,10] This congenital lung disorder typically presents as intractable early hypoxemic respiratory failure and severe PH refractory to supportive treatment.[11] Histopathologic lung parenchymal findings are characteristic on biopsy (Figure 1),[9,11-13] and recent postmortem studies suggest that abnormal arterial and venous bronchopulmonary anastomoses drive intrapulmonary right to left shunting, bypassing the alveolar-capillary bed.[14] Early genetic testing should be considered in preterm and term infants with atypical pulmonary hypertension presentation to look for mutations or deletions in the forkhead box F1 gene (FOXF1) gene. ECMO may prolong survival to allow time for biopsy, genetic testing and can be considered in selective cases as a bridge to lung transplantation.[9,12] Timely diagnosis is key to avoid unnecessary care. In most cases, death occurs in the neonatal period or early infancy.[9,10]

Severe PH due to diazoxide therapy for CHI is thought to be a rare adverse effect seen in 2% to 4.8% of patients.[15,16] Diazoxide is a benzothiadiazide-derivative that activates ATP-sensitive potassium channels (K_{ATP}) and suppresses insulin release from the pancreatic beta islet cell. Direct toxic vascular reaction and K_{ATP} channel agonism have been proposed as possible mechanisms of diazoxide-induced PH. Severe diazoxide-related adverse effects are dose-dependent, result from volume overload,[17] and direct pulmonary hypertensive effect.[15,18] The sodium and fluid retention may worsen pre-existing PH and contribute to the reopening of the ductus arteriosus.[19] Diazoxide is the only therapy approved by the U.S. Food and Drug Administration (FDA) for CHI.[20] Sequential echocardiography, concurrent administration of thiazide diuretics, and the lowest effective diazoxide dosage are strategies that can allow successful initiation or re-administration of diazoxide in CHI concomitant PH.

Hypercapnia with partially compensated metabolic alkalosis at presentation, and again upon extubation, indicated the diagnosis of Ondine's curse, or primary

Table 1. Characteristics and Unique Features Pulmonary Hypertension Cases.

Characteristics and unique features pulmonary hypertension cases

	Clinical classification of PH[9]	Mechanism of PH	Neonatal presentation	Cardiac volume load	Diagnostic features	Diagnostic testing	Genetic findings	Treatment
Vein of galen malformation	2.1	Cerebral AVM with left-to-right shunt	Yes	Yes	Cranial bruit, diastolic flow reversal in aortic arch and neck vessels	Echocardiography, brain ultrasound/ MRI	RASA1 ENG/ ACVRL1	CHF management, endoscopic embolization
Alveolar capillary dysplasia	3.5	Pulmonary capillary dysplasia with right-to-left shunt	Yes	No	Respiratory distress at birth, poor response to O_2/iNO	Biopsy/autopsy, genetic testing	FOXF1	ECMO as bridge to transplant
Diazoxide induced (CHI)	1.3	Water and salt retention, vasoactive effect	No	Yes	Treatment with diazoxide for CHI	Diuretics, trial off medication	N/A	Diuretics (thiazides), supportive care
Congenital hypoventilation syndrome	3.4	Central apnea, intermittent hypoxemia, hypercapnia	Yes	No	Hypercapnia with (partially) compensated metabolic alkalosis	Non-ventilated blood gas, genetic testing	$PHOX_2B$	Tracheostomy, ventilation, ±, phrenic nerve pacing

Abbreviations: AVM, arteriovenous malformation; CHF, congestive heart failure; CHI, congenital hyperinsulinemia; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; O_2, oxygen; MRI, magnetic resonance imaging.

congenital central hypoventilation syndrome (CCHS) in case 4. This condition is ascribed to variable types of heterozygous $PHOX_2B$ gene mutations.[21,22] Affected children lack the perception of dyspnea in response to elevated CO_2 levels but maintain voluntary breathing control. They have minimal to no ventilatory sensitivity to hypercapnia and variable ventilatory sensitivity to hypoxemia during sleep. While awake, these patients have absent ventilatory responsiveness to hypercapnia and hypoxemia.[23] Exposure to chronic, intermittent, hypercapnic hypoxemia is reported to induce erythropoiesis,[24] right ventricular hypertrophy, and PH.[25] Some present later in childhood with hypoxia, cyanosis, and right heart failure as the first indications of CCHS, leading to PH and cor pulmonale.[23] Early recognition and treatment of CCHS with adequate mechanical ventilation can reverse hypoxemia-induced PH.[20]

While the differential diagnosis of PH is broad and age-dependent, few cases present with severe PH refractory to standard management. A high index of suspicion is required when assessing for atypical causes of PH, including idiopathic and familial PH, postcapillary lesions such as pulmonary vein stenosis, alveolar capillary dysplasia, hepatic and cerebral arteriovenous malformations, iatrogenic drugs such as diazoxide as well as hypoxia-induced PH from cases like congenital central hypoventilation syndrome.[1]

Conclusion

Clinicians caring for infants with severe or refractory PH should differentiate transient PPHN from atypical etiologies of PH, based on clinical presentation, imaging findings, and initial management response. Echocardiography is a helpful noninvasive test that should be standard during the initial screening of PH. The pediatrician who cares for neonates and infants should be familiar with rare and often severe presentations of PH to provide appropriate counseling and timely treatment.

Author Contributions

MAJ, PN, DM, and RG contributed to the design, data collection, critical review and to the writing of the manuscript.

Declaration of Conflicting Interests

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