Case Report

Pulmonary Circulation

Placental vascular maldevelopment, intrauterine growth restriction, and pulmonary hypertension

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Abstract

A 33-year-old gravida 2, para 1 woman was noted to have early intrauterine growth restriction at 22 weeks gestation and subsequently developed severe pre-eclampsia. She delivered a 460 g male neonate at 28 weeks. The infant was managed on non-invasive ventilatory support and was gaining weight on enteral feeds for the first eight weeks of life, at which point he developed necrotizing enterocolitis. He then developed severe pulmonary hypertension that was refractory to maximal medical management. He died at 10 weeks of life due to hypoxemic respiratory and heart failure. Placental pathology revealed a constellation of findings consistent with maternal vascular malperfusion. Lung autopsy revealed muscularized and hypertrophied pulmonary arterioles consistent with severe pulmonary hypertension. Von Willebrand factor immunofluorescent staining of autopsy specimens suggest parallels in extent of endothelial injury. This case study illustrates our evolving knowledge of the fetal origins of neonatal lung diseases.

Keywords

developmental lung biology, neonatal lung disease and bronchopulmonary dysplasia, pregnancy

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Case description

A 33-year-old gravida 2, para 1 woman was referred to obstetrical triage at 28 weeks, 0 days gestation for severe intrauterine growth restriction (IUGR) with absent end-diastolic flow on umbilical arterial Doppler ultrasound. Estimated fetal weight was <400 g. Maternal serologies were all negative. Group B streptococcal status was unknown. Membranes were ruptured at delivery. First trimester screening for aneuploidy was risk-reducing. TORCH workup was not pursued as IUGR was attributed to severe pre-eclampsia. In obstetrical triage, blood pressure was 184/104. She received labetalol and one dose of betamethasone four hours prior to delivery. She underwent cesarean section and delivered a live-born male infant at 28 weeks weighing 460 g (birth weight-for-gestational age <<1st percentile). Apgar scores were 5 and 8 at 1 and 5 min, respectively. The infant was vigorous but with poor air movement bilaterally and was provided positive pressure ventilation by bag-mask ventilation. He began breathing spontaneously with decreased respiratory distress and was transferred to the NICU on non-invasive continuous positive airway pressure (CPAP). Initial chest x-ray demonstrated clear lungs with minimal hyaline membrane disease. No surfactant was given because he was not intubated.

He remained on nasal CPAP (PEEP: 6, $FiO_2 < 0.3$) until day of life (DOL) 35, when he was noted to have increased work of breathing and oxygen requirement. X-ray demonstrated increased perihilar/interstitial opacities and mild hypoinflation. Respiratory support was changed to (non-invasive) nasal intermittent positive pressure ventilation (NIPPV; PIP: 24, PEEP: 7, rate: 40). Blood and urine

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cultures were collected and broad spectrum antibiotics started. His first echocardiogram was performed and was notable for mild biventricular hypertrophy and patent foramen ovale (PFO) with left to right flow and no evidence of elevated pulmonary pressures or patent ductus arteriosus. He achieved full feeds by DOL 19. His weight, though below the first percentile (Z-score –3.5), tracked consistently with his postmenstrual age. He remained stable on NIPPV until DOL 49, when he was transitioned back to nasal CPAP (PEEP 7).

At DOL 57, he had increasing work of breathing and was transitioned back to NIPPV. Sepsis/infection was ruled out. Repeat echocardiogram revealed right ventricle dilation and hypertrophy, bidirectional shunting across the PFO, flattened interventricular septum, and mild tricuspid valve regurgitation with peak gradient 66 mmHg. The patient was intubated for the first time ever and placed on conventional ventilation (5 mL/kg tidal volume, Pmax: 24, PEEP: 7, rate: 40). X-ray demonstrated increased bilateral interstitial opacities.

At DOL 61, he passed a bloody stool and abdominal x-ray revealed pneumatosis consistent with medical necrotizing enterocolitis (NEC). Bowel rest and broad-spectrum antibiotics were started. He continued to require escalating ventilator support (PEEP: 8, PIP: 26, FiO_2: 0.6). Repeat echocardiogram at DOL 64 demonstrated bowing of the interventricular septum into the left ventricle and continuous right-to-left flow across the PFO, consistent with worsening pulmonary hypertension (PH). Inhaled nitric oxide was initiated at 20 ppm. Over the following three days, he required increased FiO_2 to 1.0. On DOL 67, he was muscle-relaxed and transitioned to high frequency ventilation (mean airway pressure ~16 cm H_2O). Repeat echo revealed worsening RV hypertrophy, dilation, and bowing into the LV. With ongoing consultation by the PH team, milrinone, sildenafil, norepinephrine, and inhaled treprostinil were added and titrated over the following 24–48 h. Despite these measures, the patient's gas exchange and oxygenation continued to decline, and at DOL 74, he developed bradycardia with poor perfusion and died despite resuscitative efforts. His parents provided written consent for autopsy and publication of this case.

The placenta was submitted to pathology for routine gross and histologic evaluation within 24 h after birth. Placental weight was small-for-gestational age (108 g, expected placental weight 210–331 g). Three-vessel umbilical cord was noted. Histology revealed evidence of maternal vascular malperfusion (MVM), specifically mural hypertrophy of membrane arterioles (Fig. 1g), persistent muscularization of basal plate arteries (Fig. 1h), and accelerated villous maturation with sparse, poorly vascularized villi (Fig. 1b).[1]

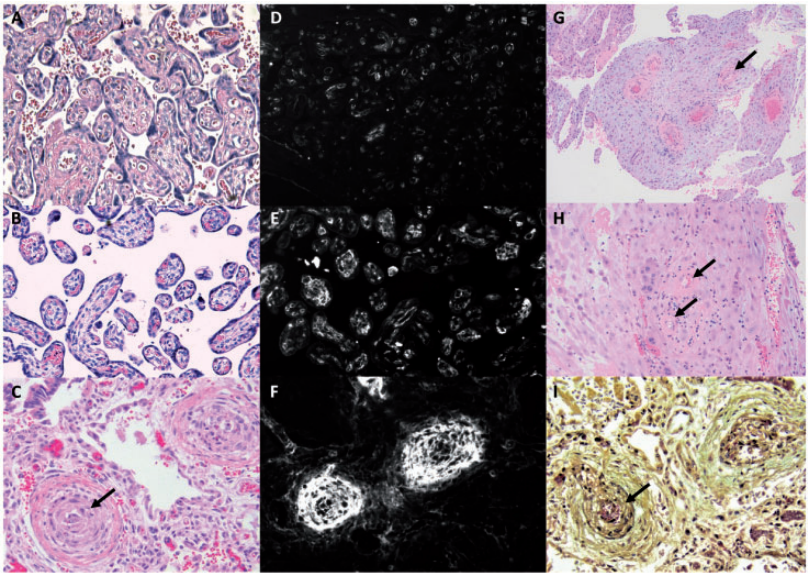

Fig. 1. (a) Hematoxylin and eosin (H&E)-stained section of control placenta (fetal side, healthy full-term birth) showing abundant, highly vascularized chorionic villi. (b) H&E-stained section of the case placenta showing sparse, poorly vascularized chorionic villi. (c) H&E-stained section of lung tissue showing prominent intimal fibroplasia of small and medium-sized arterioles and arteries (arrow). (d) Immunofluorescent staining of a representative healthy full-term control placenta with antibodies for von Willebrand factor (vWF), a marker of endothelial injury. (e) Immunofluorescent staining of the index case placenta with antibodies for vWF showing intense fluorescence of chorionic villi. Despite the increased intensity of fluorescence indicating endothelial injury, vascular density appears reduced. (f) Immunofluorescent staining of lung tissue with antibodies for vWF showing disruption of pulmonary vascular endothelium. (g) H&E-stained placental section showing mural hypertrophy of membrane arterioles (arrow), with marked thickening of the walls of parietal decidual arterioles. (h) H&E-stained placental section showing persistent muscularization of basal plate arteries (arrow), which are abnormally small, muscularized arteries within the basal plate (decidual vessels) with thick muscular walls. These lesions represent failure of normal spiral artery remodeling during early placental development. (i) Movat stain of lung tissue in image (c) highlighting the intimal fibroplasia around the pulmonary vessel walls.

Lungs at autopsy were noted to have thickened alveolar septae, alveolar simplification, and hyaline membrane formation. Findings of established, advanced pulmonary vascular disease were present and included intimal fibroplasia of arterial branches (Fig. 1c and i) and thickened muscular arterioles in interalveolar spaces. Cardiac examination was notable for biventricular hypertrophy, with right ventricular wall thickness of 0.6 cm (normal estimated 0.3 cm for age) and left ventricular wall thickness of 0.7 cm (normal estimated 0.42 cm for age).

Additional immunofluorescent staining of the placenta and lungs was performed with von Willebrand factor (vWF) to explore relative vessel density and disruption of vascular endothelium (Fig. 1d–f). Staining of the chorionic villi qualitatively showed increased vascular density in a control placenta (Fig. 1d) as compared to the case (Fig. 1e), while increased intensity of the signal in the case placenta demonstrated endothelial disruption consistent with previous reports of pre-eclamptic placentas.[2] Infant lung tissue from a healthy control was not available; however, vWF immunofluorescence of the case infant's lungs shows dramatic endothelial disruption in pulmonary arterioles (Fig. 1f). Qualitatively, there were sparse small arterioles identified by vWF staining (not shown).

Discussion

This is the case of a pregnancy complicated by maternal preeclampsia, severe IUGR, and neonatal course complicated by bronchopulmonary dysplasia (BPD), a second-hit (inflammatory) insult of NEC, and subsequent severe, refractory PH at 36 weeks postmenstrual age. Placental pathology had features of MVM, including placental growth restriction, decidual vessel pathology, and villous changes. Autopsy revealed hypertrophied and muscularized pulmonary arterioles with intimal fibroplasia consistent with advanced PH disease.

BPD-associated PH is a serious complication of prematurity, and PH incurs a four-fold increased risk of mortality over BPD alone. Postnatal factors such as inflammation, oxygen exposure, and mechanical ventilation contribute to ongoing pulmonary alveolar and vascular maldevelopment after birth.[3] Before birth, the intrauterine environment may also play a role in the development of BPD and PH.

Direct associations between IUGR, BPD, and PH have been reported.[4,5] IUGR is a complex process with numerous etiopathologies, and placental insufficiency is a well-described cause.[6] Comparison of placental pathology and lung disease has shown that severe MVM and distinct sublesions of MVM, as well as decreased villous vascularity are associated with BPD-PH.[7–9] In ovine models, lungs of growth-restricted fetuses have alveolar simplification and decreased vascular density similar to human BPD. In IUGR sheep, pulmonary artery endothelial cells demonstrate decreased proliferative capacity in response to growth factors.[10] Nuclear factor-κB expression, important in fetal pulmonary angiogenesis, is reduced in pulmonary artery endothelial cells isolated from IUGR fetal sheep.[11]

This case illustrates mirror images in placental and pulmonary histopathology that support common mechanisms of vascular development, and possible links between placental and pulmonary vascular growth. The role of the placenta as an early predictor of neonatal PH is supported. Research on the fetal programming of cardiopulmonary disease is ongoing.

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Conflict of interest

The author(s) declare that there is no conflict of interest.

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Ethical approval

Case reports are not human subjects research and not subject to IRB approval. Written consent was provided by the patient's mother.

Guarantor

Karen Mestan.

Contributorship

M.M. and K.M. drafted and edited the manuscript. M.B. and M.A. provided images of gross and microscopic pathology with descriptions and analysis. M.M. and R.B. performed special staining of placental and lung tissues. M.P. provided methodological guidance and analysis of tissue immunofluorescence.

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