



Neonatal Pulmonary Interstitial Glycogenosis-Challenging Diagnosis

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Abstract

Bronchopulmonary Dysplasia (BPD) represents the most common cause of Interstitial Lung Diseases (ILD) in premature neonates; yet, other rare causes of ILD, such as, Pulmonary Interstitial Glycogenosis (PIG) need to be considered, especially in non-intubated neonates with persistent respiratory distress and oxygen dependency. We report a case of pulmonary interstitial glycogenosis that was diagnosed in a 31-week gestation infant after exclusion of infectious etiologies. This case highlights the importance of considering PIG, which is potentially treatable cause of ILD; however, it still carries a challenging diagnosis in any neonate with persistent dependency of respiratory support that is out of proportion to the presumed diagnosis, after exclusion of infectious and cardiovascular etiologies.

Keywords: Interstitial lung disease; Pulmonary interstitial glycogenosis; Open lung biopsy

Abbreviations

RDS: Respiratory Distress Syndrome; ILD: Interstitial Lung Disease; PIG: Pulmonary Interstitial Glycogenosis; BPD: Bronchopulmonary Dysplasia; CPAP: Continuous Positive Airway Pressure; NIPPV: Non-Invasive Positive Pressure Ventilation; HRCT: High Resolution Computed Tomography; PPRM: Preterm Premature Rupture of Membranes

Introduction

Interstitial Lung Disease (ILD) is a rare group of disorder in children. The prevalence is estimated to be 0.36 per 100,000 in the pediatric population ages 0 to 16 [1]. Pulmonary Interstitial Glycogenosis (PIG) is a type of interstitial lung disease uniquely seen in infancy, first described in 2002 by Canakis et al. [2] in seven cases. Although PIG is rare, we speculate that it may be under recognized in neonates because histological examination is required to establish the diagnosis, which carries higher morbidities risks during post-operative course after the open lung biopsy. It is important to consider interstitial lung disease and PIG in neonate with early onset respiratory distress and persistent symptoms or oxygen dependency, in the context of the appropriate radiological findings.

Case Presentation

This is a 31-weeks old premature baby girl, born to a 23-year old primigravida lady. Mother has gestational diabetes mellitus that was controlled by diet only; pregnancy was complicated with PPRM. Prophylactic antibiotics were administered at this time concurrently with one dose of corticosteroids, just before delivery. Baby was delivered by normal vaginal delivery, was Appropriate for Gestational Age (AGA), having birth weight of 1,230 grams (on the 27th percentile), head circumference of 25 cm (on 28th percentile), and length of 38 cm (On 39th percentile). She cried soon after birth, but had decrease oxygen saturation with labored breathing; hence, CPAP was applied, with PEEP of 5 cm H₂O, at age of one minute of life. APGAR scores were 5 and 8 at 1 and 5 min, respectively. The baby's condition did not require intubation, or surfactant administration. Blood gases were initially acceptable, additionally, chest X-ray on day 1 of life, showed mild RDS-like picture (diffuse reticular-nodular infiltrates, Figure 1). Blood cultures were obtained and empiric treatment with ampicillin and amikacin was initiated. All cultures showed no bacterial growth. The baby's condition required respiratory support to maintain oxygen saturation, alternating between CPAP and Nasal cannula, till 6 weeks of age; with persistent tachypnea and subcostal retractions, infectious and cardiac causes were ruled out by multiple negative blood cultures and normal echocardiograph. Therefore, suspicion of Interstitial Lung Disease (ILD) was raised, as the picture of RDS and BPD was out of proportion to baby's condition and gestational age, and the fact that the baby never

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Figure 1: Initial chest X-ray showing diffuse reticulonodular infiltrates.

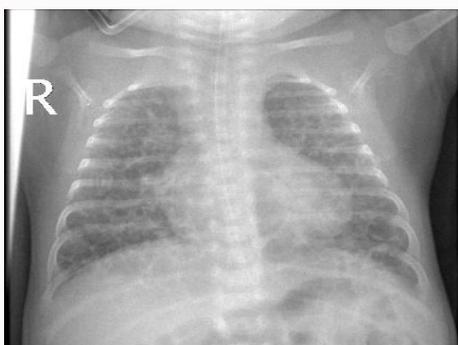


Figure 2: Progressive diffuse reticulonodular infiltrates, representing honey-comb like appearance.

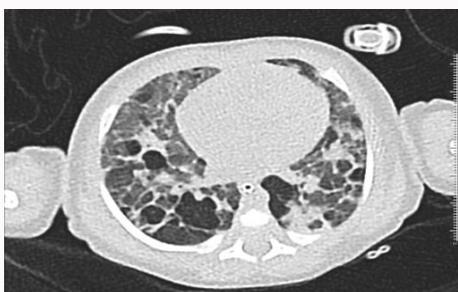


Figure 3: HRCT chest, axial image, bilateral diffuse extensive interstitial thickening (as indicated by arrows) with diffuse areas of ground-glass opacification.

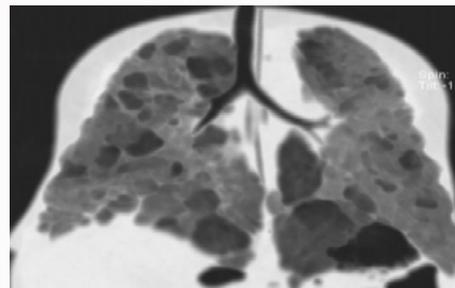


Figure 4: HRCT chest, coronal reconstructed image showing bilateral diffuse extensive interstitium thickening (as indicated by arrows) with diffuse areas of ground-glass opacification involving all lung lobes.

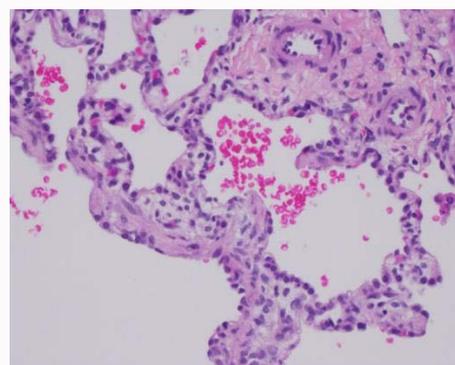


Figure 5: Wedge lung biopsy at high power (40x) demonstrates expansion of the interstitium with nucleated cells with clear cytoplasm (as indicated by the arrow).

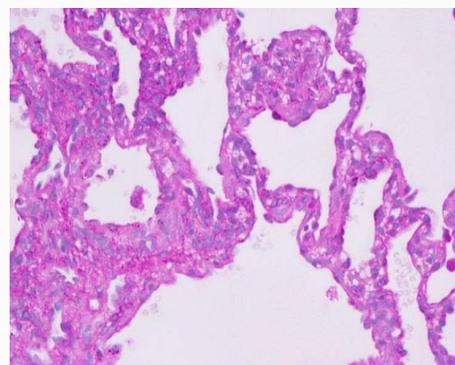


Figure 6: PAS stain shows interstitial cells containing PAS-positive material (red-purple) in the cytoplasm (as indicated by arrow).

required intubation. Additionally, worsening serial chest X-rays showing diffuse interstitial lung disease with hyperinflation (Figure 2) and accumulation of Carbon Dioxide (CO₂) in blood, reaching 55 mmHg to 65 mmHg, suggested a progressive diffuse lung disease with signs of chronic lung disease. High resolution chest CT at day 50 of life, confirmed the findings on radiograph, showing bilateral diffuse extensive interlobular septal and peribronchovascular interstitium thickening with diffuse areas of ground-glass opacification (Figure 3 and 4). At this point, our differential diagnoses included PIG, BPD, and surfactant deficiency. We opted for lung biopsy for definitive diagnosis. On day 75 of life, a wedge biopsy of the lower lobe of the right lung was performed. Post-operative course was rough, complicated with pneumothorax, total lung collapse and surgical emphysema. The baby required intubation and mechanical ventilation for 3 days. Histological findings of the lung tissue demonstrated expansions of interstitium with rather bland nucleated cells with clear cytoplasm. No evidence of marked fibrosis or features suggestive of surfactant

deficiency. Periodic Acid Schiff (PAS) stain shows glycogen present within the interstitial clear cells, which is labile to Periodic Acid-Schiff Positive Diastase (PASD). Features were consistent with Pulmonary Interstitial Glycogenosis (PIG) (Figures 5-7). Echocardiogram was done and showed mild pulmonary hypertension, that was absent on a previous echocardiogram. A diagnosis of PIG was confirmed and treatment with monthly corticosteroids (Intravenous pulse Methylprednisolone, 20 milligram/kilogram, daily for 3 days) was initiated. The child's symptoms significantly improved after glucocorticoids therapy was initiated and we were able to wean from respiratory support after the second course of corticosteroids. Whole exome sequence was obtained mainly to rule out genetic causes, such as surfactant deficiency, however, analysis revealed homozygosity for c.5 C; a variant of uncertain significance in HPS5 (Hermansky-Pudlak

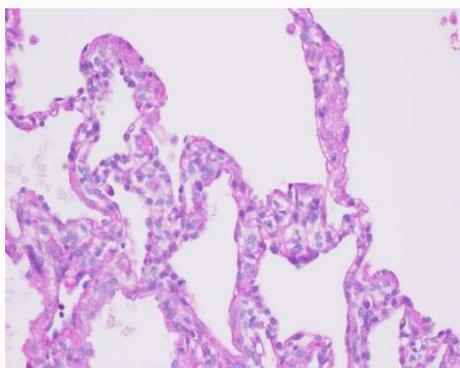


Figure 7: PASD stain shows absent staining of the interstitial cells in the cytoplasm, representing Glycogen (as indicated by arrow).

Syndrome) gene. Baby was discharged at age of 142 days after 3 doses of corticosteroids. She was sent on home oxygen with minimum flow of 1 Liter per minute; with a plan to continue the monthly steroids for 6 months and a close follow up by home-care team.

Discussion

Interstitial Lung Disease (ILD) is a rare group of disorder in children. The prevalence is estimated to be 0.36 per 100,000 in the pediatric population ages 0 to 16 [1]. Pulmonary Interstitial Glycogenesis (PIG) is a type of interstitial lung disease uniquely seen in infancy, first described in 2002 by Canakis et al. [2] in seven cases. Since the first description in 2002, PIG has been increasingly recognized in pediatric lung biopsies. Still, the true incidence of PIG is unknown due to the need of histological confirmation *via* lung biopsy. PIG can occur in term babies as well as premature babies [3]. Since PIG phenotype can be found in lung biopsies of children of all gestational ages, this suggests that the abnormality originates in utero [4]. It usually presents within the first 24 h of life in the neonatal period with tachypnea, respiratory distress and oxygen requirements out of proportion to the clinical situation or gestational age. It can also complicate the course of children with congenital heart disease with persistent pulmonary hypertension, resulting in lack of response to inhaled nitric oxide [5]. The etiology and underlying pathophysiology of PIG are still unknown. Multiple case reports and reviews postulate that PIG is caused by dysmaturity of the interstitial cells or aberrant lung development, rather than inflammatory process. Deutsch et al. [5] found that 40% of 46 lung biopsies with principle diagnosis of lung growth abnormality also had patchy PIG changes. While Langston et al. [6,7] found that nearly 60% of infants with growth abnormalities had patchy PIG. Onland et al. [8] also described PIG in monozygotic twins which may represent genetic etiology. But the twins had twin-twin transfusion syndrome which may also indicate a reactive process [8]. The detected variant in HPS5 gene in our case has never been reported in cases of PIG. The gene represents Hermansky-Pudlak Syndrome that is characterized by oculocutaneous albinism, a bleeding diathesis and, in some individuals, pulmonary fibrosis, granulomatous colitis, or immunodeficiency [9]. Apart from pulmonary involvement, our patient didn't represent any other signs and symptoms of that syndrome, which may indicates a co-incidental finding, but still might be related to the ILD reported in our case. PIG is diagnosed histologically by the presence of spindle and round, glycogen-filled, cells that widen the interstitial walls [6,7]. Electron microscopy is the most reliable diagnostic method to demonstrate the diagnostic deposits of intracellular glycogen and occasionally lipid,

which have led some to assume that these cells may be lipofibroblasts [6,7]. There is no consensus treatment guideline for PIG yet. Treatment is mainly supportive. Some cases resolve without any treatment. Intravenous pulse corticosteroid therapy was used in some patients for 6 up to 11 months with improvement in oxygenation and symptoms. Mechanism of improvement with corticosteroids is not clear. The reported response to glucocorticoids by Canakis et al. [2] was attributed to acceleration of lung maturity rather than anti-inflammatory effect. In Deutsch et al. [5] reported case, follow-up biopsy specimen at two months of age demonstrated resolution of the pathology.

Prognosis

PIG has a more favorable prognosis compared with other causes of ILD, with few reported mortalities in the absence of accompanying morbidities. Prognosis is more dependent on the overall clinical picture than on the presence of PIG alone. In the case series by Canakis et al. [2] six out of seven infants survived. The exception was a 25-week premature baby with bronchopulmonary dysplasia. No mortality has been seen in pure diffuse PIG but deaths have occurred in the presence of growth abnormalities and pulmonary hypertension [2-5].

Conclusion

Although PIG is rare, we speculate it may be under recognized in neonates because histological examination is required to establish the diagnosis. It is important to consider interstitial lung disease and PIG in neonate with early onset respiratory distress, persistent symptoms and oxygen dependency, in the context of the appropriate radiological findings. PIG is believed to be caused by aberrant lung development. However, further research needs to be done to determine the etiology and less invasive mode of diagnosis. Additional research is needed to investigate the potential correlation between PIG and HPS5 gene. Prognosis of PIG is favorable, depends on the overall clinical picture and the associated comorbidities. Most cases showed response to corticosteroids.

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