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Pulmonary Maturation Arrest and Death in a Patient With Pulmonary Interstitial Glycogenosis

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Summary

We present the clinical presentation and pathological findings from a term infant with atypical neonatal lung disease. A full term Caucasian male presented at birth with signs of respiratory distress. The respiratory condition continued to deteriorate despite maximum intervention and the patient was placed on ECMO for further cardiorespiratory assistance. An open lung biopsy demonstrated findings consistent with severe lung growth abnormality with non-uniform pulmonary interstitial glycogenosis. The patient consequently developed a pulmonary hemorrhage that required discontinuation of ECMO. The patient died shortly after decannulation. Most literature suggests that PIG is one of the few pediatric interstitial lung diseases that has a favorable prognosis with rare mortality in the absence of co-morbidities. However, the current case suggests prognosis may depend more on the underlying diagnosis than on the histological finding of PIG. In addition, this case may provide insight into the pathogenesis and potential modifiers of this idiopathic disorder.

Keywords

pulmonary interstitial glycogenosis; interstitial lung disease; pediatric; neonatal lung disease

INTRODUCTION

Pulmonary interstitial glycogenosis (PIG), also referred to as infantile cellular interstitial pneumonitis, is a rare idiopathic lung disorder unique to infants and young children.¹ Although patients with PIG often present with respiratory distress requiring prolonged supplemental oxygen or mechanical ventilation, the literature supports a good clinical prognosis for patients with isolated PIG without co-morbidities.² While the etiology and underlying pathogenic mechanisms of PIG are unknown, histopathologically the disease is characterized by the presence of glycogen laden mesenchymal cells within the interstitium of the lung.^{1,2} Questions remain whether the primary cause of PIG involves isolated aberrant differentiation of pulmonary mesenchyme or if the presence of these cells reflects a secondary, nonspecific reaction to another disease entity or pulmonary insult.

Here we present an infant with PIG and pulmonary maturational arrest. This case report suggests that morbidity is increased when PIG is associated with other conditions, and supports the hypothesis that PIG is a reactive process to select co-morbidities.

CASE REPORT

A 3,020 g Caucasian male was born to a 14-year-old Gravida 1 with an unremarkable pregnancy at 37⁴/₇ weeks gestation via caesarean-section for failure to progress. Apgars were 8 and 9, at one and 5 min, respectively. At birth, the patient required stimulation, suction, and blow-by oxygen for duskiess. Chest radiograph revealed moderate bilateral lung haziness with normal chest expansion (Fig. 1). The respiratory status continued to deteriorate despite supplemental oxygen as demonstrated by increased work of breathing, hypoxemia, and signs of pulmonary hypertension. Ultimately, the infant required intubation, administration of surfactant, mechanical ventilation, and inhaled nitric oxide by 6 hr of life, in addition to ampicillin, gentamicin, and hydro-cortisone. On day of life 2, the patient failed maximal ventilatory support and was placed on extracorporeal membrane oxygenation (ECMO) for further cardiorespiratory assistance. Repeat chest radiographs demonstrated diffuse pulmonary opacities consistent with atelectasis or edema. Cardiac ECHO showed normal heart anatomy, with a large persistent ductus arteriosus and patent foramen ovale, with suprasystemic pulmonary hypertension. There was still no pulmonary improvement after 7 days of ECMO. Immediately following numerous attempts to take the patient off ECMO, oxygenation remained normal, whereas arterial carbon dioxide levels increased to >80 mm Hg. A bronchoscopy was performed that demonstrated normal airway anatomy. On day of life 10, an open lung biopsy was performed to assist with diagnosis. Histologically, the lung tissue demonstrated dilated airways with lack of secondary septation (Fig. 2A). The alveolar interstitium was widened by non-uniform collections of cells with round to oval nuclei, vacuolated cytoplasm and indistinct cell borders (Fig. 2B,C). In addition, the interstitial cells were positive for vimentin (not shown) and PAS (Fig. 2D). Type II pneumocytes were positive by surfactant immunohistochemistry. The alveolar capillaries demonstrated normal position, and mild medial hypertrophy of the pulmonary arteries was identified. Bacterial and fungal cultures were negative. The final histologic diagnosis was severe growth abnormality with non-uniform pulmonary interstitial glycogenosis.

The lung biopsy resulted in development of a hemothorax that could not be controlled with chest tubes. Due to indication of lung abnormalities from the biopsy, the decision was made to discontinue ECMO and its necessary anticoagulation in an attempt to control bleeding into the chest. The infant developed refractory respiratory acidosis and hypercapnia, and life support was withdrawn. An autopsy was performed for definitive diagnosis.

DISCUSSION

PIG is a rare idiopathic lung disorder diagnosed after demonstration of characteristic histological findings on lung biopsy. The disease entity defining feature of PIG is the diffuse accumulation of mesenchymal cells in the alveolar interstitium without evidence of inflammation, but the etiology and pathogenic mechanisms of the disease remain unknown.^{1,2} While PIG has classically been described as an isolated finding in a neonate with respiratory distress, our patient uniquely presents the characteristic clinical and histological findings of PIG with the additional finding of abnormal lung growth. The co-existence of PIG along with a lung growth abnormality may provide insight into the pathogenesis of this disease.

Thought to be a new variant of interstitial lung disease in the neonate, PIG was first described in seven infants by Canakis et al.¹ The patients in that report demonstrated some

clinical and histological findings similar to the initial course of the patient we describe. Our patient developed respiratory distress and hypoxemia on day of life 1, requiring mechanical ventilation, as did the majority of the patients (5 of 7) reported by Canakis. Deutsch et al.² also describes six of seven patients with PIG presenting with hypoxemia at birth, similar to our patient.

The pathogenic mechanisms of PIG remain unknown. The histopathological finding of diffuse, uniform interstitial thickening due to the presence of immature spindle-shaped interstitial cells found in our patient was similar to other author's descriptions. Since this phenotype can be found in lung biopsies of patients of all gestational ages (25–40 weeks), it is suggested that this lung abnormality originates in utero.

Debate exists as to whether this accumulation of abnormal mesenchymal cells within the interstitium of the lung reflects a non-specific reactive process in the lung, such as that associated with abnormal lung development or injury, or if this accumulation reflects a developmental abnormality with aberrant differentiation. No authors suggest an indication of an inflammatory process. While the lung growth arrest present in our patient differs from the PIG cases originally described by Canakis, in a multi-institutional review of lung biopsies, Deutsch found that 19 of 46 lung biopsies with the principle diagnosis of a lung growth abnormality also had patchy changes consistent with PIG.² The characteristic findings of PIG have also been found in patients with pulmonary hypertension and vascular abnormalities.³ These examples would support a reactive process. On the contrary, Onland described interstitial glycogenosis in monozygotic twins and suggested a disturbance in a developmental pathway with a genetic component as the etiology.⁴ However, these twins also had twin-to-twin transfusion syndrome which is known to cause adaptive and maladaptive responses in the fetus.^{5,6} Acknowledging that the twins in Onland's case most likely had other co-morbidities, this would suggest they belong in the reactive process group.

Whereas there are currently no guidelines for the treatment of PIG, administration of glucocorticoids has been recommended and has shown a favorable outcome in patients with PIG.^{3,4} Clinically and anecdotally patients improve, but similar to the uncertainty as to the etiology, the mechanism of steroid therapy is unclear. It is believed that steroid therapy may exert its effect by acceleration of glycogenolysis, as well as hastening the maturational process of the lung and surfactant production. The only reported case of histologic resolution that can provide some insight into the means of steroid therapy demonstrated diminished proliferation of interstitial cells as well as apoptosis.³ However, the reported progressive improvement while on steroids may simply reflect the natural course of a self-limited disease. Despite the literature on positive prognosis, it is intriguing that our patient is only the third reported death and the first full term death with evidence of PIG.^{1,7} The death of our patient can be rationalized if the theory that PIG is a reactive process is true. With this assumption, the severity of the underlying injury or defect that "induces" the accumulation of abnormal mesenchymal cells should predict outcome rather than the presence of PIG alone. In other words, prognosis is more dependent on the overall clinical picture than the histological finding of PIG. The extreme lung dysmaturity present in our patient is most likely the cause of death, rather than the "reactive" interstitial glycogenosis, and steroids would not have induced the degree of lung maturation needed in this patient.

In conclusion, our understanding of the etiology, pathogenesis, and prognosis of pulmonary interstitial glycogenosis continues to evolve. We provide further support for a non-specific reactive process theory of ontogeny, but further investigation beyond case reports is needed to thoroughly define this disorder. The acknowledgement of the frequent presence of co-

morbidities can also help practitioners to develop therapy guidelines and prognostic details, as investigators are discovering PIG is increasingly associated with negative outcomes.

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Fig. 1. Anterior-posterior chest radiograph of case patient. The child is intubated, and a nasogastric tube, UVC, and UAC have been inserted. Radiograph shows bilateral chest haziness.

Fig. 2. (A,B) Diffuse alveolar septal thickening and airspace widening (H&E, 10 $\times$) which is indirectly highlighted by pankeratin accentuation (Cytokeratin AE1/AE3, 10 $\times$). (C,D) The interstitial widening is due to cells with round to oval nuclei with vacuolated cytoplasm and indistinct cell borders (H&E, 60 $\times$) and strongly PAS-positive (arrows, PAS, 60 $\times$).