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Original contribution

Pulmonary interstitial glycogenosis associated with a spectrum of neonatal pulmonary disorders ☆

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Summary Primary or isolated pulmonary interstitial glycogenosis (PIG) is a rare disease presenting as tachypnea and hypoxemia during the perinatal period. A diffuse interstitial infiltrate with focal hyperinflation is visible on chest imaging. The biopsy findings include diffuse expansion of the interstitium by spindle-shaped cells with pale cytoplasm that, on electron microscopy (EM), are poorly differentiated mesenchymal cells containing abundant monoparticulate glycogen. This glycogenosis appears to be a transient abnormality, usually with a favorable prognosis. Recently, cases of PIG, some associated with other pulmonary or systemic abnormalities, have been described. The clinical significance and potential role of PIG changes remain unknown. We report 28 cases of PIG associated with a spectrum of pediatric pulmonary and cardiovascular disorders, including arterial hypertensive changes with and without abnormal alveolar development (n = 9), congenital heart disease (CHD; n = 4), hyperplasia of pulmonary neuroendocrine cells resembling neuroendocrine hyperplasia of infancy (NEHI, n = 5), congenital pulmonary airway malformation (n = 5), congenital lobar emphysema (n = 4), and Noonan syndrome (n = 1). In all cases, PIG was confirmed by positive periodic acid–Schiff (PAS) staining, immunopositivity for vimentin, and EM. Although some patients improved with age, 7 died of respiratory failure or complications of CHD, suggesting that PIG may be clinically significant when associated with other severe disorders. The association of PIG with a spectrum of mostly congenital lung disorders supports its origin as a developmental abnormality of interstitial fibroblast differentiation rather than a nonspecific reactive process.

1. Introduction

Pulmonary interstitial glycogenosis (PIG) is a rare pediatric interstitial lung disease affecting mostly neonatal infants. We have reported 7 infants with PIG presenting between 1 day and 1 month of age having tachypnea and hypoxemia, with diffuse interstitial infiltrates and overinflated lungs on chest

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radiographs [1]. The lung biopsies from all cases showed similar pathology characterized by diffuse expansion of the interstitium by spindle-shaped cells with pale cytoplasm that was periodic acid–Schiff (PAS) positive but diastase labile, indicating the presence of glycogen. Immunohistochemistry staining showed that these interstitial cells contained vimentin, a general marker of mesenchymal cells, but were negative for leukocyte common antigen, lysozyme, and other macrophage markers, ruling out an inflammatory/immunologic reactive process. Electron microscopy (EM) revealed primitive interstitial mesenchymal cells having few cytoplasmic organelles indicative of fibroblast differentiation. Significantly, the cytoplasm of these cells contained abundant monoparticulate glycogen. Although cytoplasmic glycogen is normally seen in pulmonary epithelial cells during fetal lung development, it is absent from interstitial cells in postnatal human and primate lungs [2,3].

In our original series, 5 patients were treated with pulsed corticosteroids, in one case with the addition of hydrochloroquine. Although 6 of the 7 infants showed favorable clinical outcomes, one infant died from complications of extreme prematurity and bronchopulmonary dysplasia. Hence, PIG has emerged as a new variant of neonatal interstitial lung disease with a transient clinical course and a generally favorable prognosis [4,5].

Additional cases of primary/isolated PIG were subsequently reported, including an occurrence in identical twins [6]. Although the majority of reported cases have been described in otherwise normal lungs, diffuse, patchy, or focal aggregates of glycogen-containing interstitial cells have been identified in conjunction with other pulmonary disorders, notably lung growth/alveolar abnormalities, pulmonary hypertensive changes, congenital heart disease, hypertrophic cardiomyopathy, and Noonan syndrome [7-12]. Recent reviews of large cohorts of patients with pediatric interstitial lung disease reported PIG change in as many as 40% of cases with deficient lung growth and 33% of cases with pulmonary vascular disease [5,13]. Furthermore, a recently described "fetal lung interstitial tumor" (FLIT) shows extensive areas of PIG changes in the interstitium [14]. The etiology and clinical significance of PIG changes remain unknown, although some authors suggest that PIG represents a "bystander" or a reactive lesion of questionable clinical importance [15].

Here, we report 28 cases of PIG in association with a variety of mostly congenital heart or lung lesions that were observed at our institution during the past 20 years. Our findings support a hypothesis that PIG change reflects a congenital defect characterized by abnormal cell differentiation restricted to the pulmonary interstitial fibroblast lineage. Furthermore, given the recognized association of PIG with different pulmonary and cardiovascular conditions, it could represent a sentinel lesion indicative of a more generalized congenital abnormality affecting the developing mesenchyme in both the pulmonary and cardiovascular systems.

2. Materials and methods

Over a 20-year period (1996-2016), 28 cases of lung disorders/diseases with coincident diffuse or focal PIG were identified in the files of the Division of Pathology, The Hospital for Sick Children (Table; Supplementary Tables 1-4). These cases included 10 that had been referred for consultation from other pediatric institutions across Canada and abroad. The cases reported in our original series are not included in the present report [1]. Follow-up information was available for most cases with the exception of 5 of the referred cases. A review of the clinical information, diagnostic imaging results, and pathology findings was approved by the Hospital for Sick Children Research Ethics Board. The patients' ages ranged from 3 days to 8 months, and there were 16 male and 12 female patients. On the basis of clinical and pathology findings of PIG and associated pulmonary or systemic abnormalities, the cases were assigned to one of 4 main categories, as summarized in the Table, with detailed information on individual cases provided in Supplementary Tables 1-4.

For histopathologic studies, all samples (lung biopsies or surgical resections) were fixed in 10% neutral buffered formalin and embedded in paraffin. The sections were stained with

Table Demographic and clinical data

Category of PIG	Age at presentation:	Sex	Outcome
I. Abnormal alveolar development and/ or vasculopathy (n = 9)	16 d–6 mo (mean 10.3 wk)	6 M, 3 F	Died, 6; N/A, 3
II. CHD, genetic defect and vasculopathy (n = 5)	5 d–6 wk (mean 2.4 wk)	2 M, 3 F	Died, 4; discharged and lost to follow-up, 1
III. NEHI and vasculopathy (n = 5)	3 wk–3 mo (mean 7.6 wk)	3 M, 2 F	Alive with residual disease, 3; N/A, 2
IV. Congenital lung malformations (n = 9)			
CPAM-type I (n = 5)	3 d–4 wk (mean 8.8 wk)	2 M, 3 F	Improved, doing well postoperatively, 5
CLE (n = 4)	4 wk–8 mo (mean 11.6 wk)	3 M, 1 F	Improved, doing well postoperatively, 3; complications related to CHD, 1

Abbreviations: CHD, congenital heart disease; CLE, congenital lobar emphysema; CPAM, congenital pulmonary airway malformation; N/A, not available; NEHI, neuroendocrine hyperplasia of infancy.