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Spectrum of Lung and Cardiovascular Diseases in Association with Pulmonary Interstitial Glycogenosis

Rose Chami*

Division of Pathology, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada

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***Correspondence:**
Dr. Rose Chami, Division of Pathology, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; Email: rose.chami@sickkids.ca

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Keywords
Infants
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Hyperplasia of pulmonary neuroendocrine cells
Mesenchymal cells

Abstract

"Pulmonary Interstitial Glycogenosis (PIG) associated with a spectrum of neonatal pulmonary disorders", reported by Cutz et al represents one of the largest series published to date. The report included twenty-eight cases of lung or cardiac disorders with coincident diffuse, patchy, or focal PIG reviewed in Division of Pathology, The Hospital for Sick Children. The authors focused on reporting a spectrum of disorders associated with PIG and described four clinicopathological subgroups including imaging, ultrastructural findings, and clinical outcome. The present paper highlights the main findings reported by Cutz et al, and a review of literature is also presented.

PIG is a rare interstitial lung disease of infancy that is placed in the category of "specific conditions of undefined etiology" in the childhood interstitial lung disease (ChILD) classification (1). PIG has been reported mainly in either pre-term or full-term babies younger than six months of age (2, 3). Infants with PIG usually present with persistent tachypnea and hypoxemia shortly after birth or in the first few weeks of life (3, 4, 5). The reported PIG cases have been described in otherwise normal lungs (isolated/diffuse or patchy pattern)

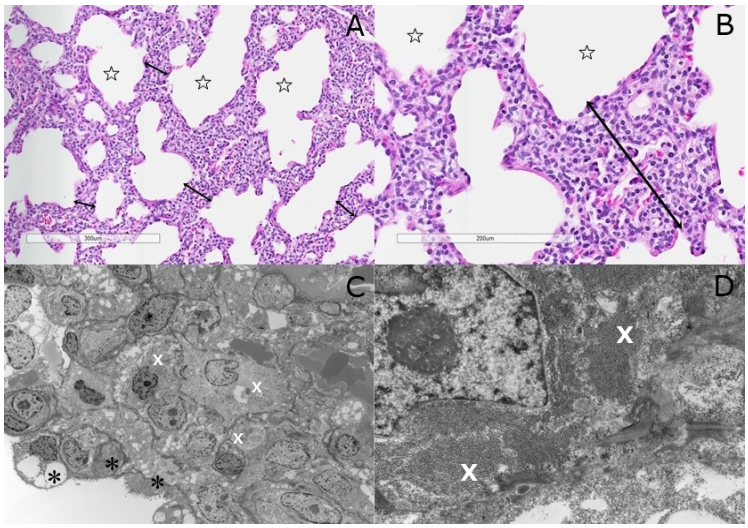

Figure 1: (A) Abnormal enlarged alveoli (stars) with diffuse interstitial thickening (double head arrows) with mesenchymal cells [H&E stain]; **(B)** Interstitial mesenchymal cells with pale cytoplasm (H&E stain); **(C)** Mesenchymal cells with rare organelles and abundant monoparticulate glycogen in cytoplasm (white X) and pneumocytes type II (black Asterix) [Transmission EM]; **(D)** Close-up view of PIG cells with pools of glycogen (white X) [Transmission EM].

(3, 5) or often in conjunction with other cardiovascular or pulmonary abnormalities (2, 3, 6, 7). To the best of my knowledge, approximately 78 cases of patients with PIG (not including the cases published by Cutz et al) have been reported in the literature with variable information regarding the clinical presentation, comorbidities, imaging, histopathology, and outcome were published. The described findings are summarized in Table 1.

TABLE 1. REPORTED CASES of PIG

Authors	**N. of patients**	**GA at birth, preterm or term**	**Sex**	**Age at presentation**	**CHD**	**PHN**	**Other comorbidities**	**Lung histopathology (main findings)**	**Chest HRCT (main findings)**	**Outcome at time of last follow-up**
Liptzin et al, 2018 (6)	24	Late preterm/ term (N=18)	M (N=15) F (N=9)	Range 0.3-6 months	63 % of patients [including HLHS, PVS, ASD, VSD], PDA, TF, mitral stenosis, coarctation of aorta)	38% of patients (N=9)	Cleft lip/palate (N=2) Autism (N=1) Unilateral kidney (N=1) Neurologic deficits (N=4) Hypotonia (N=1) Seizure (N=1) Hypothyroidism (N=1) Airway malacia (N=3) Aspiration (N=1) Urinary retention (N=1) Connective tissue disease (N=1) 22q deletion (N=1)	Diffuse PIG (45.8%; N=11) Patchy PIG (45.8%, N=11) Alveolar simplification (79%, N=19) PAH (79%, N=19)	GGO (N=19) Cysts (N=11) Linear reticular opacities (N=3/22)	Off all respiratory support (N=12) Supplemental oxygen (N=8) Mechanical ventilation (N=2) Lung transplantation (N=1) Died (N=1)
Weinman et al, 2018 (10)	15	39 weeks	M	Birth	PFO, DTV	Yes	-	Diffuse PIG, PAH	GGO, cysts	Oxygen at rest
		40 weeks	M	3 months	PFO, PDA	Yes	Aspiration, autism, airway malacia	Patchy PIG, PAH, Alveolar simplification	Architectural distortion, atelectasis	Off respiratory support
		34 weeks	F	Birth	PFO, PVS	Yes	Seizures	Diffuse PIG, PAH, PH Alveolar simplification	GGO, cysts, interlobular septal thickening	Lung transplantation and oxygen at rest
		40 weeks	F	3 months	Absent	No	-	Patchy PIG, PAH	GGO, cysts	Oxygen with sleep
		32 weeks	F	Birth	Absent	Yes	Airway malacia	Diffuse PIG, PAH, Alveolar simplification	GGO, cysts, architectural distortion	Off respiratory support
		29 weeks	F	Birth	PDA	No	Airway malacia	Patchy PIG, PAH, PN Alveolar simplification	Cysts, GGO, interlobular septal thickening	Mechanical ventilation
		39 weeks	M	Birth	Absent	Yes	Airway malacia	Diffuse PIG, PAH, PH, Alveolar simplification	Air trapping, GGO	Off respiratory support
		36 weeks	M	Birth	ASD	No	-	Patchy PIG, PAH, PN, PH, alveolar simplification	Cysts, GGO, architectural distortion	Oxygen at rest
		29 weeks	M	Birth	PDA	No	-	Patchy PIG, PAH, CMV, alveolar simplification	Cysts, GGO, architectural distortion	Off respiratory support
		36 weeks	M	Birth	TF	Yes	Aspiration, septo-optic dysplasia	Patchy PIG, pleural thickening, alveolar simplification	GGO, atelectasis, PIE	Off respiratory support
		37 weeks	M	Birth	Absent	Yes	CDH	Diffuse PIG, PAH, PH, Alveolar simplification	GGO, cysts, interlobular thickening	Died

		30 weeks	M	Birth	ASD, PDA	Yes	-	Diffuse PIG, PAH, Alveolar simplification	Cysts, GGO, interlobular thickening	Off respiratory support
		40 weeks	F	Birth	ASD, PDA	Yes	Single kidney	Patchy PIG, PAH, Alveolar simplification	GGO, architectural distortion, atelectasis	Oxygen at rest
		27 weeks	M	Birth	PDA	No	-	NA	GGO, cysts, interlobular thickening	Off respiratory support
		40 weeks	F	1 month	ASD, PDA, ascending aortic dilation	Yes	CTD ACTA2 mutation, Airway malacia	NA	Cysts, GGO, architectural distortion	Off respiratory support
Seidl et al, 2018 (7)	11	Term	F	Birth	No	Yes	Mucopolysaccha-ridosis	NA	Consolidation, linear opacities, bronchiectasis	Reduced, but persistent respiratory symptoms, no oxygen demand, ±
		Term	M	Birth	PDA	Yes	Mucopolysaccha-ridosis	Diffuse PIG, mild reduced alveolarization	GGO, consolidation, septal thickening	Reduced, but persistent respiratory symptoms, no oxygen demand, ±
		Term	M	Birth	VSD, PFO	Yes	Brain (divided plexus)	Diffuse PIG, moderate reduced alveolarization	Linear opacities, consolidation	Asymptomatic
		Term	M	Birth	Absent	Yes	-	Diffuse PIG, moderate reduced alveolarization	GGO, mosaic attenuation, linear opacity, consolidation, architectural distortion	Died
		34 weeks	M	Birth	Absent	No	Encephalopathy, hepatic cysts	Diffuse PIG, mild reduced alveolarization	Hyperinflated 2ndary lobule, septal thickening	Reduced, but persistent respiratory symptoms, no oxygen demand, ±±
		Term	F	Birth	Absent	Yes	-	Diffuse PIG, mild reduced alveolarization	GGO, consolidation, mosaic attenuation, linear opacities	Asymptomatic
		30 weeks	M	Birth	PDA	No	Hypoglycemia	NA	GGO, septal thickening, crazy paving pattern, linear opacity, hyperinflated secondary lobule	Reduced, but persistent respiratory symptoms, no oxygen demand
		Term	F	Birth	Absent	Yes	-	Diffuse PIG, severe reduced alveolarization	GGO, linear opacity, bronchial wall thickening	Asymptomatic
		Term	M	7 weeks	AVSD	Yes	-	Patchy PIG, moderate reduced alveolarization	GGO, mosaic attenuation, septal thickening, emphysema	Asymptomatic
		Term	F	Birth	VSD, ASD hypoplastic pulmonary arterial system	Yes	Renal failure, megaureter (left)	Diffuse PIG, severe reduced alveolarization	NA	Asymptomatic

		Term	M	Birth	ASD, VSD, coarctation	Yes	Heterotaxy syndrome (heart, lung, abdomen)	Diffuse PIG, severe reduced alveolarization	GGO, consolidation	Reduced, but persistent respiratory symptoms, no oxygen demand, ±±
Still et al, 2018 (17)	1	Term	F	Birth	Absent	Yes	-	Patchy PIG, Alveolar simplification (moderate), PAH	Diffuse mosaic attenuation, right pulmonary artery enlargement	On low flow oxygen, multidrug regimen for persistent pulmonary hypertension
Demirel et al, 2018 (18)	1	Term	F	Shortly after birth	PDA (large), secundum ASD*	Yes	Filamin A protein deficiency, Bronchomalacia (LLL)	Patchy PIG (mild), moderate alveolar simplification and hyperinflation	Findings most consistent with Filamin A deficiency **	Supplemental oxygen, multidrug regimen for pulmonary hypertension, steroids
Deutsch et al, 2016 (19)	5	38	M	Birth	Absent	NA	-	PIG (pattern distribution NA), lung growth abnormality	NA	Persistent tachypnea, cough
		37	M	Birth	Absent	NA	Severe chylothorax	PIG (pattern distribution NA), lung growth abnormality	NA	Asymptomatic
		41	F	Birth	Total anomalous pulmonary venous return/ vein stenosis	Yes	-	PIG (pattern NA), lymphangiectasia, PAH	NA	Died
		35	F	Birth	Double outlet right ventricle	Yes	VACTERL	PIG (pattern NA), lung growth abnormality, PAH	NA	Intermittent asthma
		36	M	Birth	Absent	Yes	-	PIG (pattern NA), lung growth abnormality, PAH	NA	Asymptomatic
Sanchez-de-Toledo et al, 2015 (20)	1	Term	NA	Birth	D-transposition of great arteries with intact ventricular septum	Yes	-	PIG	NA	Successful corrective surgery, Asymptomatic
Simons et al, 2014 (21)	1	NA	F	1 month	ASD, massive window duct with right ventricular hypertrophy and pulmonary trunk dilation	NA	Aniridia	PIG, alveolar simplification	NA	Successful corrective surgery, Asymptomatic
Ehsan et al, 2014 (22)	1	Term	M	Birth	Absent	NA	-	Diffuse PIG Alveolar simplification (diffuse)	GGO (diffuse)	Asymptomatic, no oxygen demand, although FVC remained significantly reduced compared to healthy control patients
Ross et al, 2014 (23)	1	34	M	Birth	Pulmonary valve abnormalities	No	Noonan syndrome (positive test for heterozygous G60A mutation in *PTPN11*)	Diffuse PIG, Alveolar growth abnormality/ simplification, Mild acute inflammation	Septal thickening, Extensive dependent airspace opacities, Small pleural effusions	On nocturnal supplemental oxygen

Alkhorayyef et al, 2013 (16)	1	Term	M	Birth	Severe hypertrophic cardiomyopathy, PFO	Yes	-	Diffuse PIG	CT none done Chest X-ray: bilateral GGO	Died
Radman et al, 2012 (14)	2	Term	F	Birth	D-transposition of great arteries with intact ventricular septum, PFO, and large PDA	Yes	-	Patchy PIG, PAH	NA	Asymptomatic
		Term	M	Birth	Heterotaxy with complex cardiovascular abnormalities	Yes	-	Diffuse PIG, PAH (minimal)	NA	On supplemental oxygen
King et al, 2011 915)	1	Term	M	Birth	Large PDA, PFO	Yes	-	Patchy PIG, severe lung growth abnormality, PAH (mild)	NA	Died
Smets et al, 2011 (23) & 2004 (24)	1	Term		Birth	Absent	Yes	Hunter syndrome (mucopolysaccha-ridosis type II)	Diffuse PIG	Architectural distortion, linear opacities, areas of hyperinflation and GGO	Frequent upper respiratory infections, Lung function tests: severe combined obstructive/ restrictive pattern
Castillo et al, 2010 (12)	1	37	M	Birth	Absent	NA	-	Patchy PIG, Severe alveolar growth abnormality, Mild pleural thickening	GGO (diffuse), prominent interstitial opacities, multiple scattered cystic spaces	Asymptomatic
Lanfranchi et al, 2010 (26)	1	31	M	18 days of life	Absent	NA	-	Diffuse PIG	Diffuse coarse reticular opacities	Asymptomatic
Orlando et al, 2005 (27)	2 (identical twins)	31	M	Birth	Absent	No	-	Diffuse PIG	GGO, septal thickening	Asymptomatic
		31	M	Birth	Absent	No	-	Diffuse PIG	GGO, septal thickening	Asymptomatic
Canakis et al, 2002 (4)	7	33	M	5 days	Absent	NA	-	Diffuse PIG	Not done at initial presentation	Mild intermittent bronchospasm
		38	M	1 day	Absent	NA	-	Diffuse PIG	GGO, patchy (performed at 7 months age)	Mild intermittent bronchospasm
		40	M	4 weeks	Absent	NA	-	Diffuse PIG	GGO, patchy (performed at 2 years of age)	Asymptomatic
		33	M	1 day	Absent	NA	-	Diffuse PIG	NA	On supplemental oxygen
		29	F	1 day	Absent	NA	-	Diffuse PIG	NA	Asymptomatic
		40	M	1 day	Absent	NA	-	Diffuse PIG	NA	Asymptomatic
		25	M	1 day	Absent	NA	-	Diffuse PIG	NA	Died (cor pulmonale)

Abbreviations: PIG= pulmonary interstitial glycogenosis, N= number of patients, GA=gestational age, CHD=congenital heart disease, PHN=pulmonary arterial hypertension, HRCT= high-resolution computed tomography, HLHS=hypoplastic left heart syndrome, PVS= pulmonary vein stenosis, ASD=atrial septal defect, VSD=ventricular septal defects, PDA=patent ductus arteriosus, TF=Tetralogy of Fallot, NA=not available, PAH= pulmonary artery hypertrophy, GGO=ground glass opacities, PFO=patent foramen ovale, DTV=dysplastic tricuspid valve, PH=pulmonary hemorrhage, PN=pneumonia, CMV=cytomegalovirus, CDH=congenital diaphragmatic hernia, CTD=connective tissue disease, AVSD= atrial-ventricular septal defects, LLL=left lower lobe, VACTERL= vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities, FVC=forced vital capacity.

* large patent PDA, secundum atrial septal defect with left to right shunting, associated left atrial, right atrial and right ventricular enlargement, and pulmonary insufficiency with right ventricular hypertrophy. Moderate to severe pulmonary arterial hypertension.

**diffuse pulmonary hyperinflation, pruning of the peripheral pulmonary vasculature, and patchy areas of atelectasis.

± recurrent respiratory infections, reduced exercise tolerance

±± tachypnea at rest

PIG was first described in 2002 by Canakis et al (4). The definitive diagnosis is made by histologic examination. Histologic features on lung biopsy are characterized by expansion of pulmonary interstitium by round to ovoid-shaped mesenchymal cells with pale cytoplasm (fig. 1A & 1B) due to glycogen accumulation demonstrable by periodic acid-Schiff positivity (diastase sensitive) on light microscopy. However, the presence of glycogen is best identified on electron microscopy (EM). The ultrastructural examination showed poorly differentiated interstitial mesenchymal cells with vesicular nuclei and cytoplasm containing sparse organelles and abundant monoparticulate glycogen (fig. 1C & 1D). Some PIG cells showed features of differentiation toward the fibroblast lineage differentiation (2).

Additionally, 28 cases of PIG in association with a spectrum of lung or cardiac disorders have been reported recently by Cutz et al. In this paper, we described four clinicopathologic subgroups including comorbidities, imaging and outcome (summarized in Table 2). As previously reported (3, 6, 8), we found that PIG is most commonly

Table 2: List of Cases of PIG Reported by Cutz et al; Patients' Gender, Gestational Age, Comorbidities, Histopathology, Imaging Findings, And Clinical Outcome at Last Follow-Up

Category	**Patient**	**GA, preterm, or term**	**Sex**	**Comorbidity**	**Lung histopathology**	**Chest HRCT findings**	**Outcome**
I	1	Term	M	Pulmonary hypertension	AGA, diffuse PIG, PAH	NA	Died
	2	Term	F	-	AGA, patchy PIG	NA	NA
	3	32 weeks	M	-	AGA (severe), Diffuse PIG	NA	NA
	4	Term	M	Pulmonary hypertension	AGA, Diffuse PIG, PAH	GGO (diffuse)	Died
	5	Term	M	Pulmonary hypertension	AGA, Patchy PG, PAH	GGO	Died
	6	33 weeks	F	Pulmonary lymphangiectasis	AGA, Diffuse PIG, lymphangiectasia	Diffuse septal thickening, bilateral pleural effusion	NA
	7	Term	M	Congenital chylothorax	NA	NA	Died
	8	Term	F	Pulmonary hypertension, arthrogryposis	AGA, patchy PIG, PAH	NA	Died
II	9	Term	M	PDA, dilated cardiomyopathy, pulmonary hypertension	Patchy PIG, PAH (mild)	GGO (focal)	Died
	10	Term	F	Complex cardiac abnormalities (right atrial isomerism, dextrocardia, AVSD, DORV, hypoplastic RPA), pulmonary hypertension	Focal PIG, lymphangiectasis, PAH (moderate)	GGO (patchy)	Died
	11	Term	M	Hypoplastic left heart syndrome	Focal PIG, AGA, PAH (mild)	GGO	Died
	12	36 weeks	F	Noonan syndrome with hypertrophic cardiomyopathy	Patchy PIG, lymphangiectasis, PAH	Diffuse septal thickening, bilateral pleural effusion	Died
	13	Term	F	ASD, VSD, pulmonary hypertension, aspiration, pneumonia	Diffuse PIG, PAH (mild)	Diffuse lung interstitial disease	Died
	14		M	TAPVD	Diffuse PIG, AGA	GGO (diffuse, mild), septal thickening (patchy)	Successful corrective surgery
III	15	Term	M	Pulmonary hypertension	Hyperplasia of PNE cells, diffuse PIG,	"crazy paving" appearance	Off all respiratory support
	16	Term	M	Pulmonary lymphangiectasia	Hyperplasia of PNE cells, PIG, AGA, lymphangiectasia,	GGO, septal thickening, patchy hyperinflation	Off all respiratory support
	17	30 weeks	M	ASD, VSD, airway malacia, autism	Hyperplasia of PNE cells, PIG, PAH (mild)	GGO, basal hyperinflation	Off all respiratory support
	18	36 weeks	F	Pulmonary hypertension	Hyperplasia of PNE cells, patchy PIG, PAH (mild)	NA	NA
	19	Term	F	Pulmonary hypertension	Hyperplasia of PNE cells, patchy PIG	NA	NA

IV	20	Term	F	-	CPAM type I (large cyst type), patchy PIG	Multicystic lesion with air-filled, thin-walled spaces of large size in in LLL	Asymptomatic after surgical treatment
	21	Term	F	Chiari malformation	CPAM type I (large cyst type), diffuse PIG	Multicystic lesion with air-filled, thin-walled spaces of large size in RML & LLL	Asymptomatic after surgical treatment
	22	Term	F	Renal dysplasia	CPAM type I with systemic arterial supply (hybrid lesion), focal PIG	Large air-filled cystic lesion with systemic vascular supply	Asymptomatic after surgical treatment
	23	31 weeks	M	-	CPAM type I with systemic arterial supply (hybrid lesion), focal PIG	Fluid and air-filled large cystic lesion with systemic vascular supply	Asymptomatic after surgical treatment
	24	Term	M	-	CPAM type I (large cyst-type), focal PIG	Large air-filled cystic lesion	Asymptomatic after surgical treatment
	25	Term	F	CHD	CLE with focal PIG	RML hyperinflation	Cardiac complication
	26	Term	M	-	CLE with focal PIG	RML hyperinflation	Asymptomatic
	27	Term	M	-	CLE with diffuse PIG	RUL overinflation	Asymptomatic after surgical treatment
	28	Term	M	-	CLE with diffuse PIG	LUL hyperinflation	Asymptomatic after surgical treatment

Abbreviations: PIG= pulmonary interstitial glycogenosis, GA=gestational age, AGA=alveolar growth abnormality, HRCT= high-resolution computed tomography, ASD=atrial septal defect, VSD=ventricular septal defects, PDA=patent ductus arteriosus, NA=not available, PAH= pulmonary artery hypertrophy, DORV=double outlet right ventricle, hypoplastic RPA=hypoplastic right pulmonary artery, GGO=ground glass opacities, AVSD= atrial-ventricular septal defects, TAPVD=Total Anomalous Pulmonary Venous Drainage, CPAM=congenital pulmonary airway malformation, PNE cells=pulmonary neuroendocrine cells, LLL=left lower lobe, RML=right middle lobe, CHD=congenital heart disease, CLE=congenital lobar emphysema/hyperinflation, RUL=right upper lobe, LUL=left upper lobe.

associated with lung/alveolar growth abnormality, with or without pulmonary arterial hypertension. The mean age at time of biopsy was 10.3 weeks (range 16 days-6 months). This group of patients presented with respiratory distress in the first weeks of life. Most patients in our series had pulmonary hypertension. Chest imaging studies revealed variable changes such as diffuse lung interstitial thickening and ground-glass opacities. The lung biopsies showed patchy or diffuse PIG changes, and abnormal alveolarization manifested by alveolar enlargement and simplification. This group of patients had a high mortality rate with 6 of the 9 infants dying of respiratory failure within few weeks of presentation despite conventional treatment. Most infants in this group developed refractory pulmonary hypertension.

The second subgroup represented patients with PIG associated with congenital heart diseases (CHD) (including hypoplastic left-heart syndrome, hypertrophic cardiomyopathy in patient with Noonan syndrome). Chest imaging studies showed variable non-specific changes (including ground glass opacity, septal thickening). The mean age at lung biopsy was 2.4 weeks (5 days-6weeks). The PIG changes on light microscopy were focal to patchy. Most infants died of complications despite corrective surgery.

The third category consisted of a specific group of patients with combined PIG and hyperplasia of pulmonary neuroendocrine cells (PNEC), referred to as neuroendocrine hyperplasia of infancy-like (NEHI-like). Infants of this group were either pre-term or full-term, mostly presented with tachypnea and wheezing between 3 and 10 weeks of age. Chest imaging studies revealed variable changes including “crazy paving” appearance, bilateral ground-glass opacities or basal hyperinflation. Lung biopsies demonstrated patchy to diffuse PIG, and prominent hyperplasia of PNEC (identified with immunohistochemistry studies). The patients of this group were mostly asymptomatic over time with normal lung function or persistent mild obstructive defects. The clear significance and etiology of this combined pathology is unknown. PNEC system has multifaceted roles including lung development, neonatal adaptation as airway oxygen sensors, and postnatal airway homeostasis as guardians of a stem cell niche (9). Hyperplasia of PNEC has been identified in several perinatal pediatric lung disorders including bronchopulmonary dysplasia, neuroendocrine hyperplasia of infancy, central hypoventilation syndrome, Sudden Infant Death Syndrome, and cystic fibrosis (9).

The fourth and final group consisted of cases of congenital lung malformation with coincident PIG. This included 5 patients with CPAM type 1 (large cyst type) and 4 patients with congenital lobar emphysema/hyperinflation

(CLE). All patients presented with respiratory distress, soon after birth for CPAM, and between 4 weeks and 8 months of age for CLE cases. Chest imaging studies demonstrated changes related to the underlying diseases; localized cystic lesion in patients with CPAM, and lobar emphysema/hyperinflation in patients with CLE. The mean age at time of biopsy was 8.8 weeks for CPAM (range 3 days – 4 weeks), and 11.6 weeks for CLE (range 4 weeks-8 months). Pathologic examination confirmed the diagnosis of CPAM type 1 or CLE. In addition, it showed patchy PIG changes in both the lesion and adjacent <<normal>> areas of pulmonary tissue. All patients underwent lobectomy of the affected lung. Except for one case, who had CLE and congenital heart disease, patient with CPAM and CLE all recovered post-surgery and were asymptomatic on follow-up.

In summary, the spectrum of disorders in association with PIG reported by us (2) is diverse and is quite like that reported by Langston et al (3), Liptzin et al. (6), Dishop M. (8), and Weinman (10). We found that PIG is most commonly seen in association with lung alveolar growth abnormality (alveolar simplification) and / or cardiovascular diseases. We have also described additional cases of PIG associated with persistent pulmonary hypertension with or without CHD, cardiovascular disease, Noonan syndrome (23), and congenital lobular emphysema (28). In addition, we have reported a new association of PIG with other lung disorders including NEHI-like, and CPAM type 1 (large cyst type). Similarly, to previous published studies by Liptzin et al. (6), Weinman et al (10), Deutsch et al. (11), Castillo et al. (12), and Lee E. (13), we noticed that the imaging of PIG is variable, non-specific (including diffuse ground-glass opacities, hyperinflation, and cystic spaces), and is likely affected by the presence of coexisting lung disorders. Based on available literature, PIG is considered to have a favorable prognosis, although clinical outcome is dependent on the severity of any associated lung disorders or other comorbidities. In our series, we found that the mortality rate was high when PIG coincided with life-threatening comorbidities (including severe lung growth abnormality, complex cardiovascular disease). This note was also emphasized by multiple previously published reports (6, 11, 12, 14, 15, 16). In the review by Deutsch et al (16), no mortality occurred among the six cases of diffuse/isolated PIG, although respiratory symptoms persist in most patients. Given no radiographic patterns, genetic findings, or biomarkers were characteristic of PIG, the lung biopsy remains the gold standard for diagnosis.

Finally, the precise nature and clinical significance of PIG is unknown. While the pathology demonstrated poorly differentiated interstitial mesenchymal cells, there is a debate whether PIG is a primary developmental lung disorder or a reactive process to abnormal lung development and injury. Our finding of a close association of PIG with different lung developmental disorders and comorbid cardiac developmental diseases favors a defect in interstitial fibroblast differentiation. Further studies are required to define the precise pathogenesis and significance of PIG and its impact on concurrent disease processes.

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