Unusual course of hyaline membrane disease – pulmonary interstitial glycogenosis
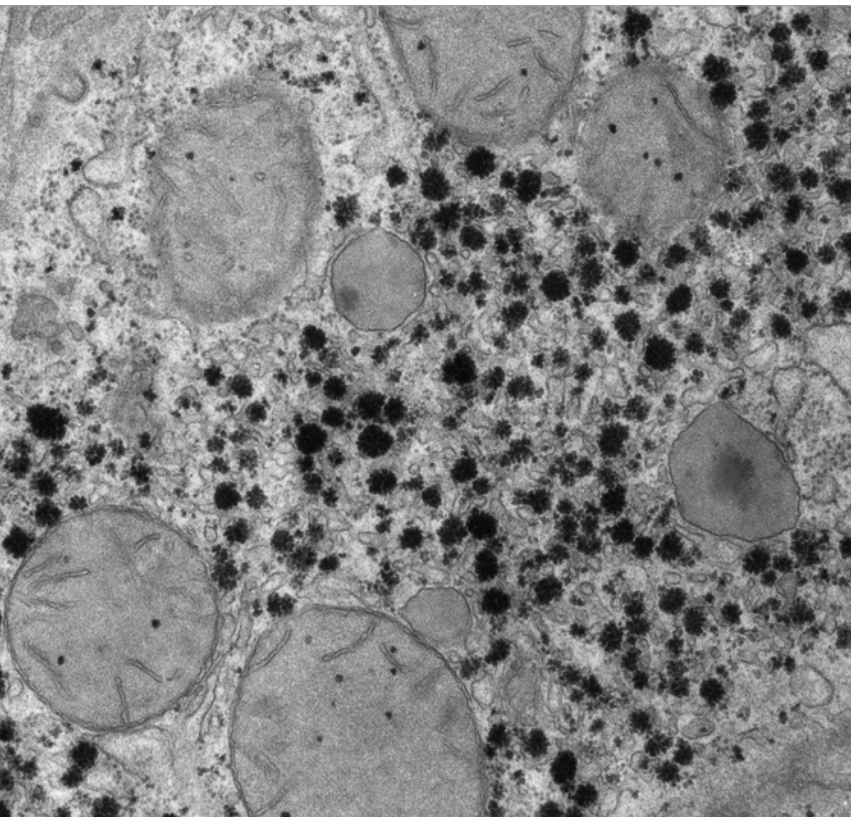
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Title figure:
TEM of glycogen deposits in rat liver
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The most common etiology of severe respiratory distress in very low gestational neonates is surfactant deficiency. Antenatal corticosteroids to enhance lung maturation, exogenous surfactant replacement therapy and various lung-protective modes of invasive and non-invasive respiratory support have revolutionized the prognosis for such infants. In contrast to infants born in the 1980s, the majority of these infants now survive without severe forms of bronchopulmonary dysplasia (BPD). In this report, we describe a VLGAN with unusually severe lung disease requiring prolonged respiratory support. The course did not correspond to typical hyaline membrane disease (HMD) and/or evolving BPD and the ultimate diagnosis could only be established by open lung biopsy.

INTRODUCTION

Fig. 1

Chest X-ray DOL 1 (age 2 hours: SIMV with FiO$_2$ 0.6, PIP 24 cmH$_2$O, PEEP 5 cmH$_2$O, rate 60 / min): despite the fact that surfactant had been administered in the delivery room, there is bilateral white-out consistent with grade IV hyaline membrane disease.

Fig. 2

Chest X-ray DOL 1 (age 8 hours: HFOV with FiO$_2$ 0.34, MAP 11 cmH$_2$O, amplitude 21, frequency 10 Hz): significantly improved aeration (right > left).

Fig. 3

Chest X-ray DOL 4 (HFOV with FiO$_2$ 0.50, MAP 12 cmH$_2$O, amplitude 26, frequency 10 Hz): worsening aeration with ground glass appearance and air bronchograms after pulmonary hemorrhage and a second dose of surfactant.

Chest X-ray DOL 5 (HFOV with FiO$_2$ 0.80, MAP 14 cmH$_2$O, amplitude 29, frequency 8 Hz): worsening aeration despite higher ventilator settings and a third dose of surfactant.

The mother, a 34-year-old G3/P1, was hospitalized at 28 4/7 weeks of gestation due to preeclampsia. A full course of antenatal corticosteroids was administered. The male infant was born to a by emergency Cesarean section at 29 0/7 weeks of gestation due to worsening preeclampsia and a retroplacental hematoma. The infant adapted well with Apgar scores of 5, 7 and 9 at 1, 5 and 10 minutes, respectively. Arterial and venous umbilical cord pH values were 7.28 and 7.35. The infant was stabilized on nCPAP and transferred to the neonatal intensive care unit. Due to worsening respiratory distress, the infant was intubated and surfactant was administered. The initial chest X-ray on conventional mechanical ventilation (SIMV) was consistent with grade IV hyaline membrane disease (Fig. 1); lung aeration improved once the infant was switched to high frequency oscillatory ventilation (HFOV) (Fig. 2).

On day of life (DOL) 4, the respiratory situation deteriorated again due to acute hemorrhagic pulmonary edema (Fig. 3). A second dose of surfactant was administered and a hemodynamic significant PDA was closed with ibuprofen. Twenty-four hours later, the patient was still requiring high ventilatory settings (Fig. 4); therefore, a third dose of surfactant was administered and, on DOL 7, a rescue attempt with hydrocortisone was undertaken. Ten days later, the patient's condition had improved remarkably and the boy could be switched from HFOV to SIMV (Fig. 5).

Because the course was felt to be extraordinary despite the infant's immaturity, genetic disorders of surfactant synthesis were sought. However, genetic analyses revealed no evidence of SP-B, SB-C or ABCA-3 deficiencies. In addition, no mutation was detected in the NKX2-1 gene which could cause brain lung thyroid syndrome.

Coinciding with weaning of the corticosteroids and growth of Enterobacter cloacae in the tracheal aspirates on DOL 26, there was again near-total white out on chest X-ray (Fig. 6). The patient was stabilized with HFOV (Fig. 7) and hydrocortisone dosing was again increased.

On DOL 35, a CT scan of the chest was obtained to determine the extent and pattern of the lung abnormalities and to plan an open lung biopsy. The results of this imaging study were non-specific and showed dense infiltrates dorsally and bilateral, diffuse ground glass appearance of the lung parenchyma with thickened septae (Fig. 8).

On DOL 38 (i.e., at a corrected gestational age of 34 3/7 weeks), an open lung biopsy was performed. Histology was characterized by partially immature lung tissue with early alveolarization and dystelectatic areas, particularly in the biopsy from the lower lobe. The main finding, however, was marked alveolar septal widening by PAS-positive interstitial cells, consistent

Fig. 5   **A**   **B**
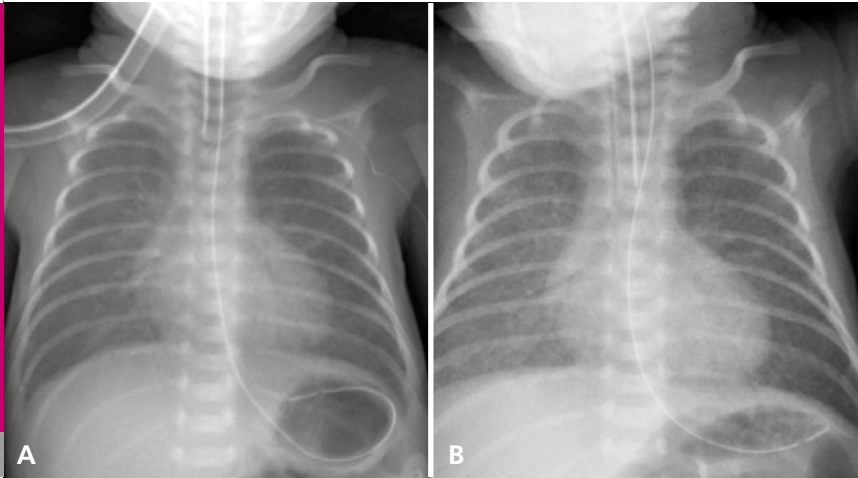
Chest X-ray DOL 17 (HFOV with FiO$_2$ 0.21, MAP 9 cmH$_2$O, amplitude 10, frequency 10 Hz): low ventilator setting following reintubation 24 hours earlier because of obstructive apnea (A: HFOV with FiO$_2$ 0.21, MAP 9 cmH$_2$O, amplitude 10, frequency 10 Hz; B: SIMV with FiO$_2$ 0.25, PIP 18 cmH$_2$O, PEEP 5 cmH$_2$O, rate 50 / min).
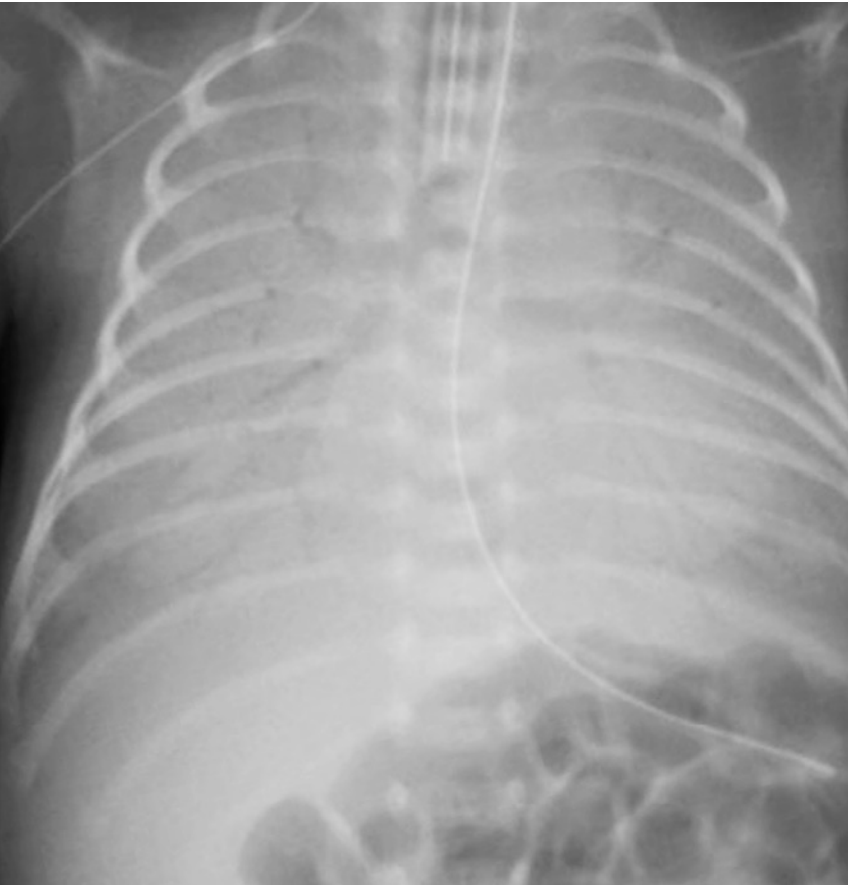
Fig. 6

Chest X-ray DOL 26 (SIMV with FiO$_2$ 0.65, PIP 19 cmH$_2$O, PEEP 5 cmH2O, rate 50 / min): near total whiteout and detection of Enterobacter cloacae in the tracheal aspirate.

Fig. 7

Chest X-ray DOL 26 (HFOV with FiO$_2$ 0.30, MAP 8 cmH$_2$O, amplitude 22, frequency 8 Hz): rapid improvement following the administration of the 4th dose of surfactant.
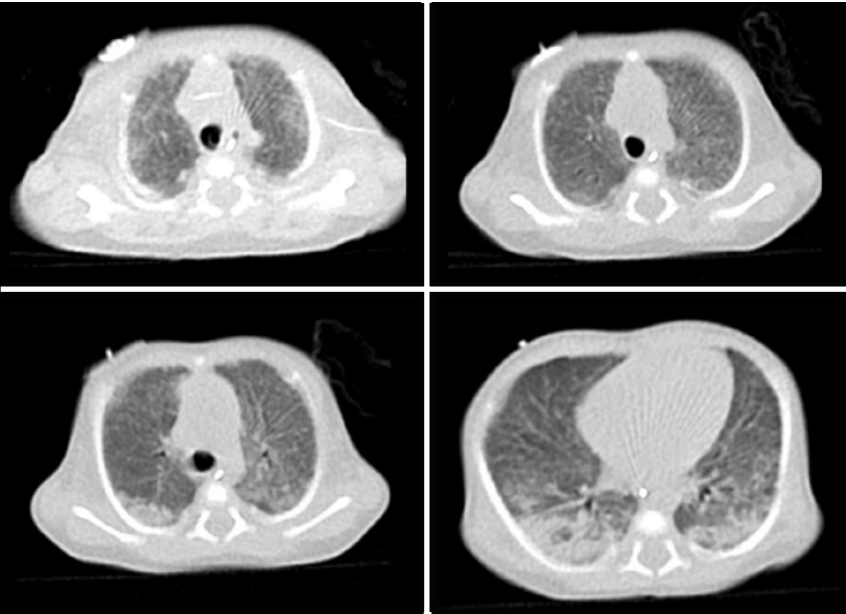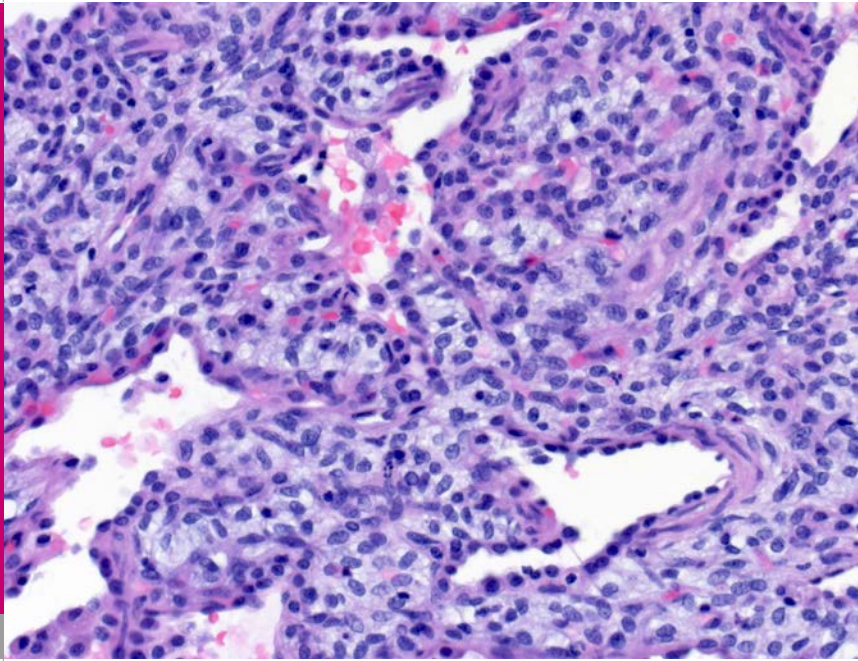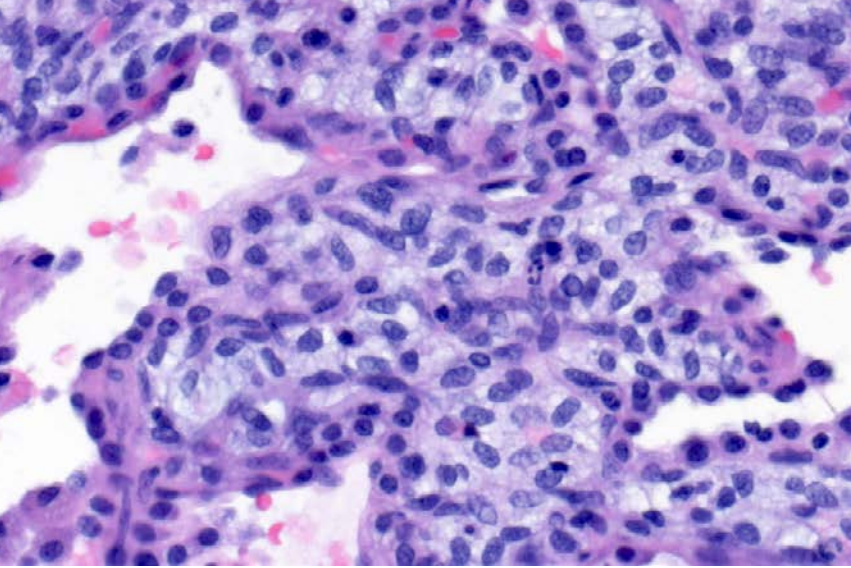
Fig. 8

CT scan of the chest DOL 35: dense infiltrates dorsally, diffuse ground glass appearance of the lung parenchyma and thickened septae.

Fig. 9

Lung histology (HE stain, low power view): marked widening of pulmonary interstitial spaces.

Fig. 10

Lung histology (HE stain, high power view): the interstitium is expanded by round- to spindle-shaped cells with pale cytoplasm.

with a diagnosis of pulmonary interstitial glycogenosis (PIG) (Fig. 9 – 12).

More than three weeks after the lung biopsy, the patient could finally be extubated to nCPAP on DOL 63. Treatment with hydroxychloroquine was begun three days later and hydrocortisone was successfully weaned. Finally, all respiratory support (including supplemental oxygen) could be discontinued on DOL 91. The patient was discharged home at a corrected age of 42 5/7 weeks while still on hydroxychloroquine. The patient's complex hospital course is summarized in Fig. 13.

On last follow-up at the age of three years, the boy had developed normally, was fully active and his physical examination was normal without any signs or symptoms of chronic lung disease. On chest X-ray there was no evidence of interstitial lung disease (Fig. 14).
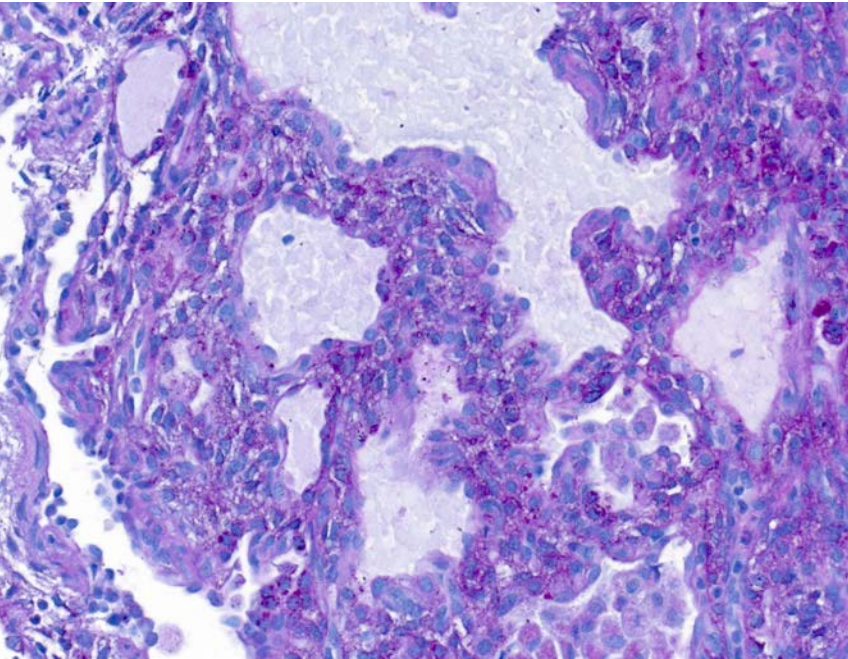
Fig. 11

Lung histology (PAS stain): the cytoplasm of the inter-stitial cells contain masses of PAS-positive material, indicative of glycogen.

Fig. 12

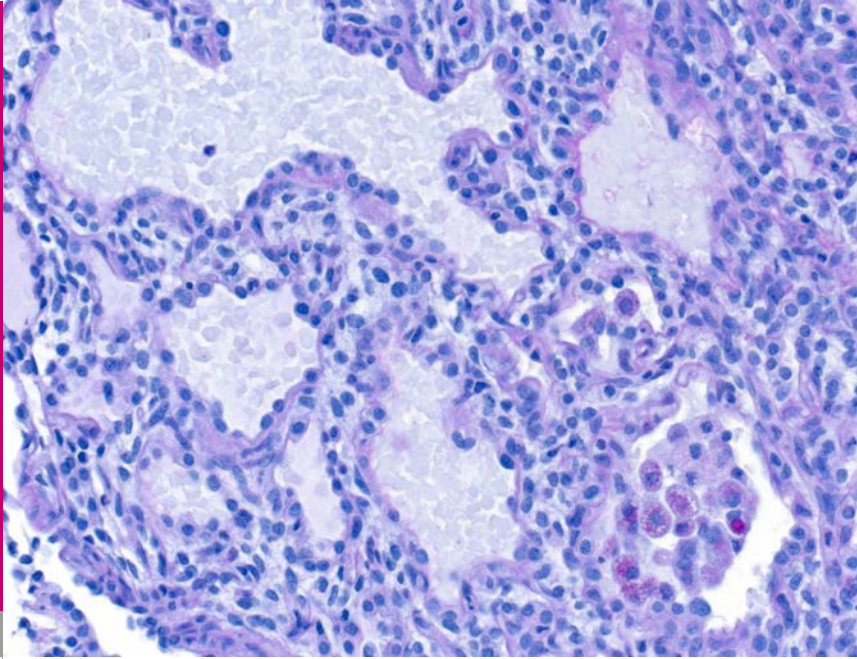*Lung histology (Diastase PAS stain): the PAS-positive cytoplasmic granules disappear after diastase treatment.*
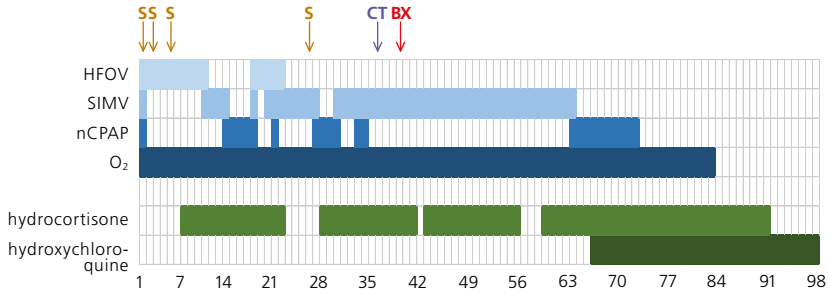
Fig. 13

Hospital course: the patient required prolonged respiratory support, four doses of surfactant and multiple courses of corticosteroids which were eventually weaned after the introduction of hydroxychloroquine (S: surfactant, CT: computed tomography of the chest, BX: open lung biopsy).

Chest X-ray at the age of three years: ne evidence of interstitial lung disease.

Children's interstitial lung disease (chILD) has an estimated prevalence of 1.3 to 3.6 / 1'000'000 (1, 2). The term refers to a heterogeneous group of rare and diffuse lung diseases associated with significant morbidity and mortality (3). ChILD syndrome requires the presence of at least 3 of the following 4 criteria in the absence of other known disorders: a) respiratory symptoms (cough, rapid breathing, or exercise intolerance), b) respiratory signs (resting tachypnea, crackles, retractions, digital clubbing, failure to thrive, or respiratory failure), c) hypoxemia, and d) diffuse infiltrates on chest X-ray or computed tomography (CT) scan (4). The diagnostic approach to patients with suspected chILD syndrome is complex and based on history, physical examination, imaging studies, pulmonary function testing, genetic testing, bronchoalveolar lavage and, in most cases, an open lung biopsy. High-resolution CT is a useful tool for demonstrating the type of abnormality, the extension and distribution of the disease, and for identifying optimal biopsy sites avoiding sampling errors when biopsies are taken randomly (4).

Pulmonary interstitial glycogenosis (PIG) was first described in 2002 by Canakis et al. (5). They found similar histopathology findings in seven patients with atypical neonatal lung disease: expansion of the interstitium by spindle-shaped cells containing periodic-acid Schiff (PAS) positive diastase labile material consistent with glycogen. Electron microscopy revealed primitive

interstitial mesenchymal cells with few cytoplasmic organelles and abundant monoparticulate glycogen.

Canakis et al. speculated that PIG appeared to be caused by selective dysmaturity of interstitial cells without apparent effects on type 2 alveolar or endothelial cell differentiation (5). Of interest, glycogen accumulation does not occur in interstitial cells during normal lung development; in contrast, it does accumulate in primitive epithelium. Thus, it has been suggested that PIG represents an aberration in lung development rather than an inflammatory or reactive process (4).

Since its first description, a number of additional case reports of PIG have been published (6 – 19). In some of these patients, PIG was the only abnormal finding (i.e., idiopathic PIG), while others had additional pathologies (e.g., congenital heart disease, lung growth abnormalities, pulmonary hypertension). In an analysis of 187 patients by the chILD Research Co-operative from the US, six patients with idiopathic diffuse PIG were reported; in addition, 19 of 46 patients with lung growth abnormalities also displayed patchy PIG (20).

Many patients with PIG have been treated with corticosteroids and most of these have shown a clinical response. It has been speculated that the beneficial effect from corticosteroid therapy results from an acceleration of the maturation process rather than from modifying inflammation (5, 19).

Prognosis of patients with isolated PIG appears to be good (19); fatal cases have only been reported in a patient with extreme prematurity and BPD (5), a patient with severe lung growth abnormality (11), and patients with severe pulmonary hypertension (12, 19).

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