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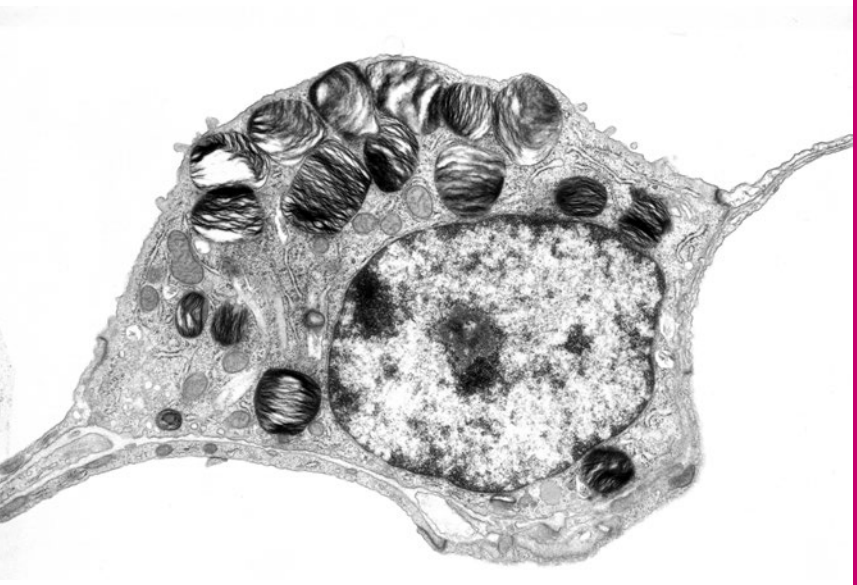
When neonatal history followed by failure to thrive leads to a rare diagnosis



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Title figure:
Type II alveolar cell with lamellar bodies
(source: http://melss.med.mun.ca/EMR)

INTRODUCTION

Failure to thrive is a common condition in pediatrics and the broad differential diagnosis should include systemic diseases.

We describe the case of a late preterm baby who had an unusually severe neonatal respiratory distress syndrome requiring prolonged respiratory support. Common digestive symptoms followed by failure to thrive led to a rare diagnosis at the corrected age of 3 months.

This late preterm twin boy was born by vaginal delivery at 35 2/7 weeks of gestation. Adaptation was unremarkable with Apgar scores of 8, 10 and 10 at 1, 5 and 10 minutes respectively; arterial and venous umbilical cord pH values were 7.33 and 7.38. Birth weight was 2320 g (P10 – 25), length 45 cm (P10 – 25) and head circumference 33 cm (P25 – 50). His twin sister never developed any symptoms remained perfectly healthy.

Minutes after birth, the boy developed respiratory distress, complicated at 2 hours of age by a right-sided pneumothorax (Fig. 1). Despite insertion of two successive chest tubes, respiratory distress persisted, leading to intubation, mechanical ventilation and transfer to a tertiary neonatal intensive care unit.

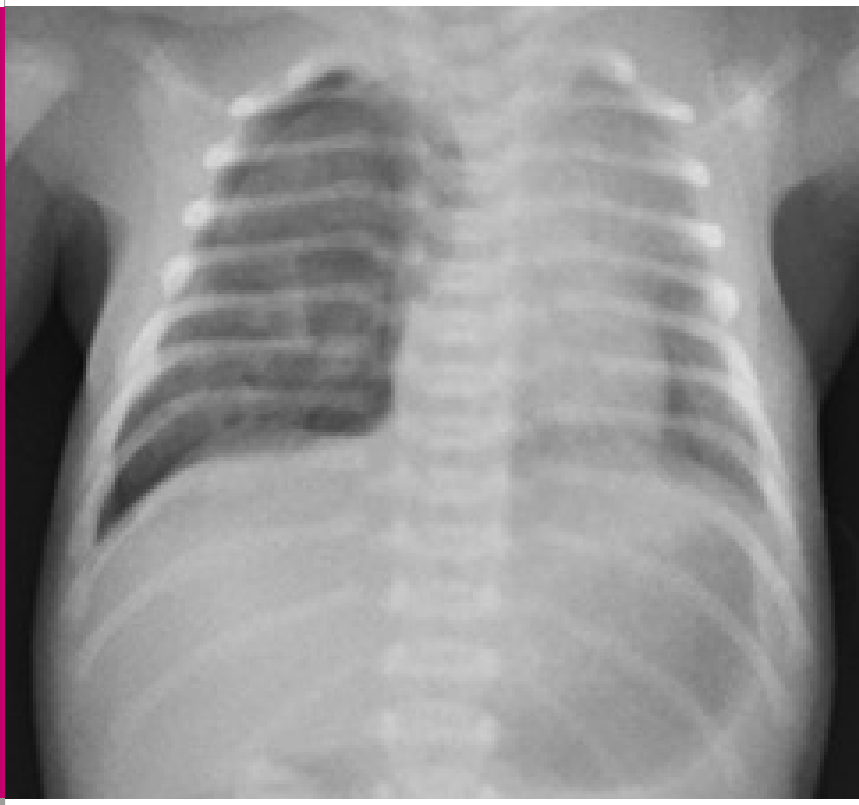

Fig. 1 *Anteroposterior chest X-ray after birth (DOL 1) showing a right-sided pneumothorax causing mediastinal shift.*

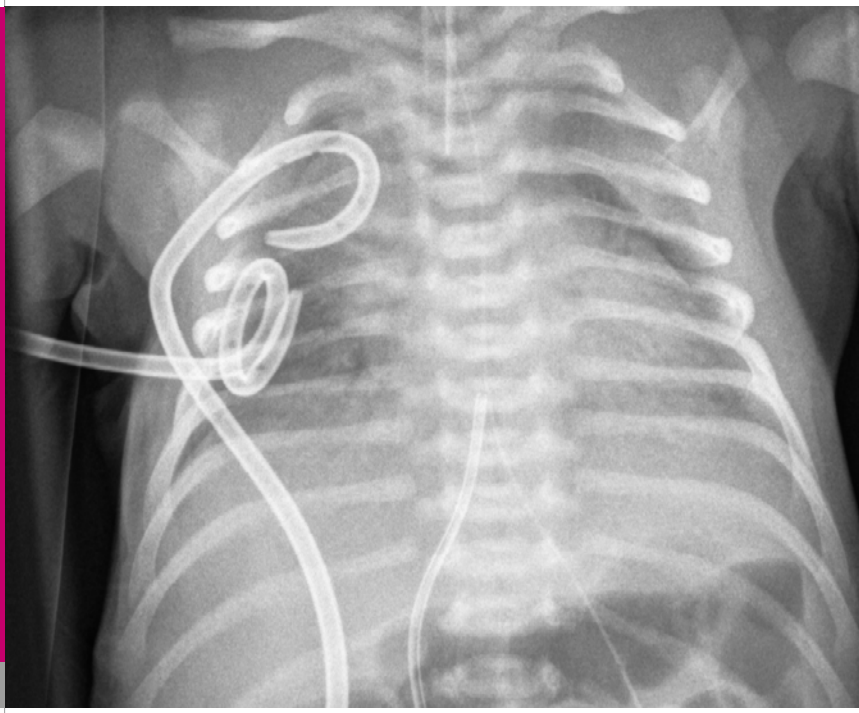

Fig. 2

Anteroposterior chest X-ray on DOL 2: almost complete reexpansion of the right lung following insertion of 2 plural drains.

On a chest X-ray obtained after admission, the lung fields were remarkable for a diffuse fine granular pattern; the two right-sided pleural drains were in proper position and there was a residual pneumothorax (Fig. 2). Even though antenatal corticosteroids had been administered at 30 weeks of gestation and despite a gestational age of 35 weeks, the findings were felt to be consistent with respiratory distress syndrome (RDS), and endotracheal surfactant was administered. Unfortunately, there was no major improvement. Conventional ventilation was changed to high frequency oscillatory ventilation with a mean airway pressure of 14 cmH_2O and a pressure amplitude of 38 cmH_2O because of respiratory acidosis (pH of 7.16 and pCO_2 of 77 mmHg). The patient remained hypoxemic despite an FiO_2 of 1.0, and persistent pulmonary hypertension was confirmed by echocardiography. Cardiovascular support with dobutamine and iNO at 20 ppm were added. The chest tubes could be removed on day of life (DOL) 2 and 3. Inhaled NO, however, had to be continued for 5 days and mechanical ventilation was required until DOL 10.

After extubation, the patient was put on nasal CPAP with PEEP of 5 cmH_2O with an oxygen requirement up to 30 % until transfer to a level II hospital close to the parents' home on DOL 23. Echocardiography on the same day no longer showed sings of pulmonary hypertension.

Repetitive vomiting and feeding problems had appeared as early as DOL 9. As both an abdominal ultrasound examination and an upper gastrointestinal contrast study were normal, cow's milk protein allergy was suspected and hydrolyzed formula feedings were started. The patient was finally discharged home on DOL 46, but he continued to have frequent regurgitations and poor weight gain. Weight at discharge was 2.9 kg (P3), length 49.5 cm (P5 – 10) and head circumference 35.5 cm (P25 – 50).

When an esophageal pH-study at 7 weeks of life revealed gastric acid reflux, treatment with a proton pump inhibitor (PPI) was started. As there was no improvement, the parents discontinued both the hydrolyzed formula feedings and PPI treatment two weeks later.

The parents reported fast breathing and cough during feeds and sleep as well as general discomfort and frequent vomiting. At 3 months of life, he was readmitted to the hospital for investigation of failure to thrive.

Clinical examination showed a pale, hypotrophic baby with axial and peripheral muscular hypotonia. Weight was 3.55 kg (P < 3, -4.6 SD), length 56 cm (P < 3, -2.5 SD) and head circumference 30 cm (P3 – 10). Respiratory rate was 70 breaths / minute; room air saturation was 97% with episodes of desaturation down to 75%

during sleep and feeds. A chest X-ray revealed increased lung volumes and diffuse ground glass appearance sparing both lung bases (Fig. 3).

The unusually severe and prolonged neonatal respiratory distress syndrome in a late preterm infant, associated with persistent tachypnea, failure to thrive and the radiological findings on conventional X-ray were highly suggestive of childhood diffuse interstitial lung disease (chILD). At this point, a chest CT was obtained and showed microcysts and diffuse ground glass opacities, supporting this hypothesis even though the pattern was not specific for a speficic diagnosis (Fig. 4, 5).

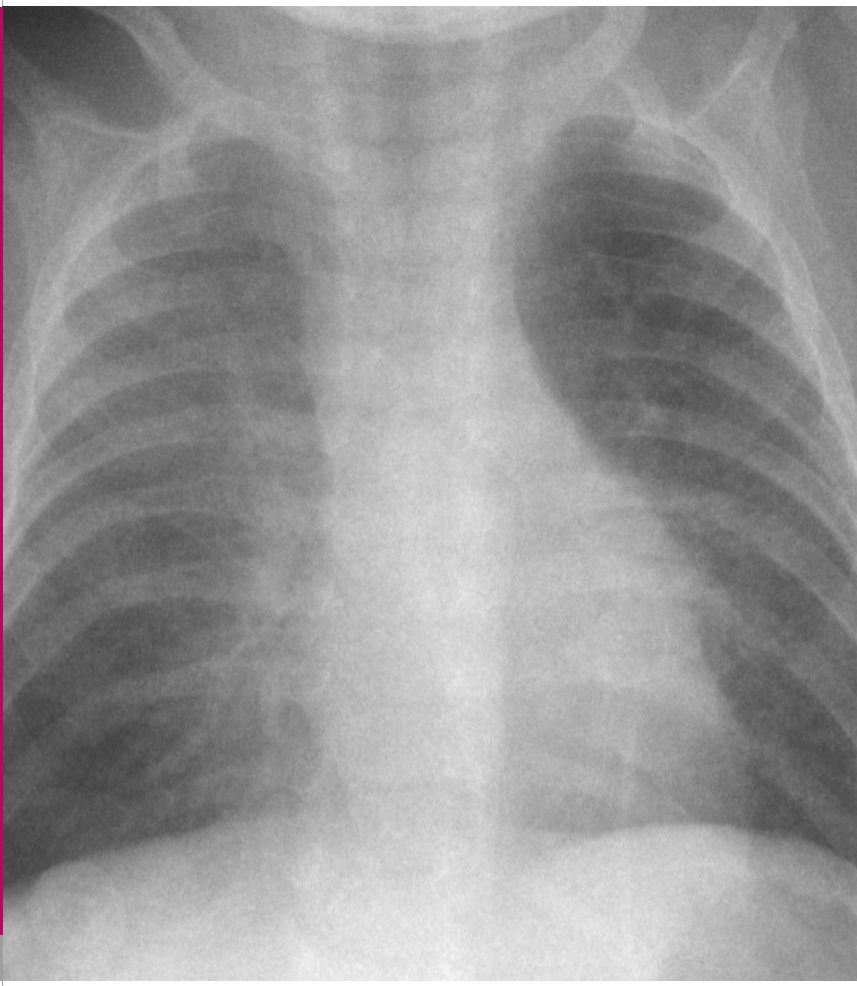

Fig. 3

Anteroposterior chest X-ray at three months of age: note bilateral increased lung volumes with diffuse ground glass infiltrates sparing both bases.

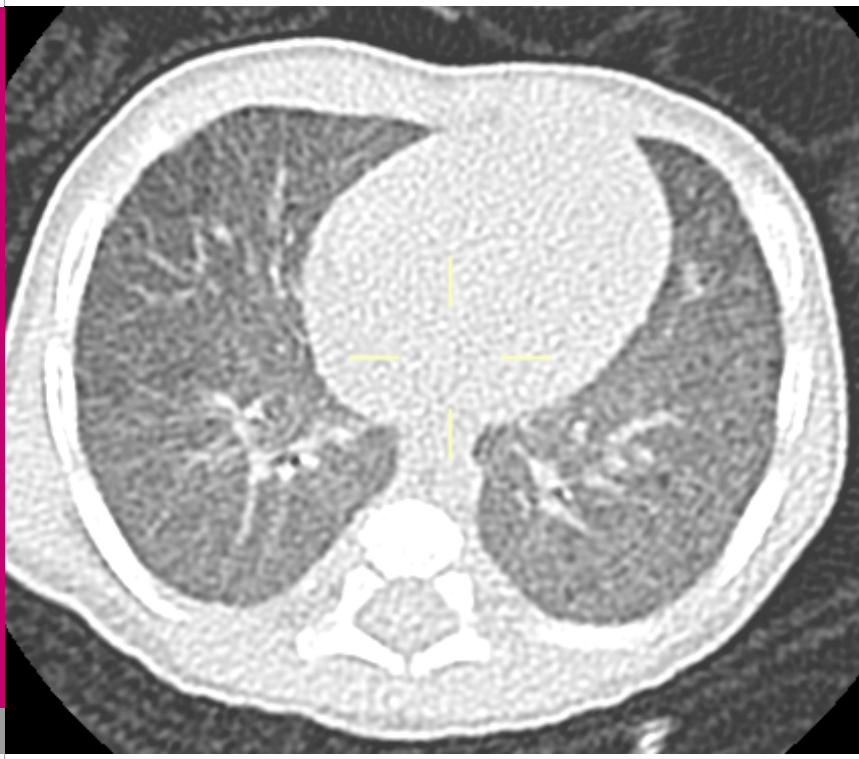

Fig. 4

Axial CT scan of the chest at the age of 3 months: diffuse, homogeneous ground glass opacity of the pulmonary parenchyma.

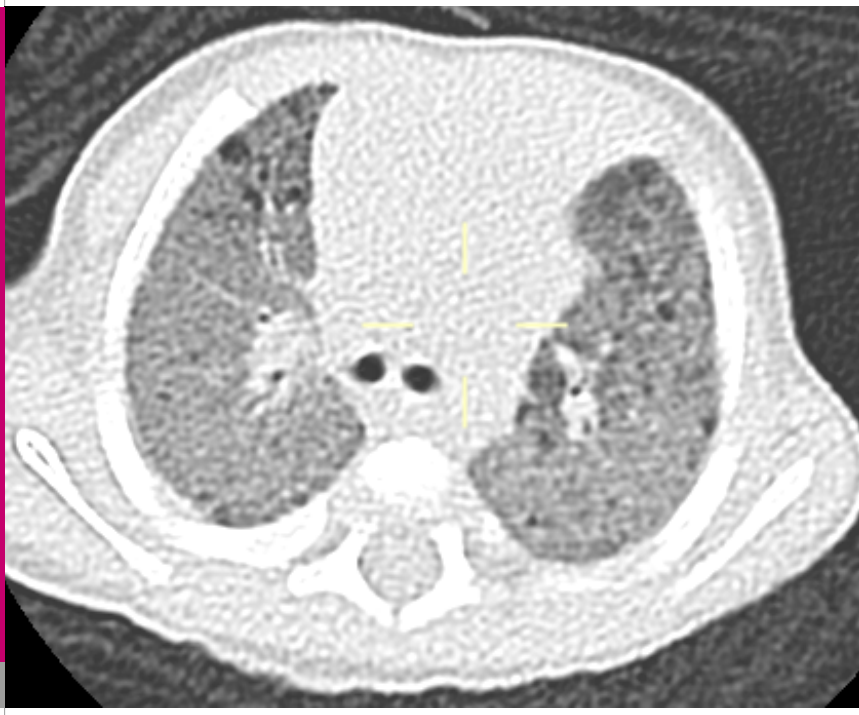

Fig. 5

Axial CT scan of the chest at the age of 3 months: development of multiple pulmonary microcysts.

The introduction of oxygen therapy by nasal cannula and nutritional optimization were followed by rapid clinical improvement with proper weight gain within days.

As ChILD is a descriptive diagnosis, many investigations are necessary to reveal its definite cause. In our case, a normal echocardiography excluded recurrence of pulmonary arterial hypertension. Complete blood count, immunoglobulin levels and a metabolic work-up were normal. On genetic analysis, no pathogenic mutations or pathological variants for coding of surfactant protein B or surfactant transport protein (testing for SFTPB and ABCA 3 genes) or for brain-lung-thyroid syndrome (testing for NKX2.1 gene) were found. Analysis of the SFTPC gene, however, revealed two polymorphisms in a heterozygous state for surfactant protein C.

Bronchoscopy revealed no anatomical abnormalities, and bronchoalveolar lavage showed normal cellularity with mild neutrophilia without any microbiological agents identified. There were no lipid-laden macrophages, thus excluding reflux-associated disease.

Finally, histology of a surgical lung biopsy done at about 6 months of age (Fig. 6, 7) showed thickening of the alveolar septae, enlarged airspaces, pneumocyte hyperplasia, focal intraalveolar macrophages and eosinophilic material, compatible with a diagno-

sis of chronic pneumonitis of infancy (CPI). Based on these findings, oral hydroxychloroquine at a dose of 8 mg / kg / day was started.

At the writing of this report, the boy was 28 months old, thriving and developing normally, but still on hydroxycholoroquine and supplemental oxygen therapy. Tachypnea had slowly resolved and hypoxemia was absent when the child was awake, short periods off oxygen therapy were well tolerated.

A follow-up chest CT scan obtained 6 months after the beginning of hydroxychloroquine treatment showed reduced ground glass opacities, and there were no signs of pulmonary hypertension on echocardiography.

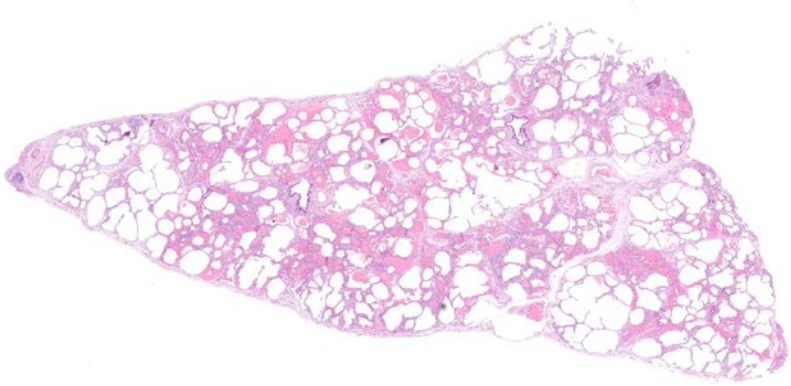

Fig. 6

Lung histology (whole mount, H&E stain) at 6 months: thickening of alveolar septae with mesenchymal cells and rare lymphocytes, enlarged airspaces, hyperplastic pneumocytes, intraalveolar hemorrhage with focal macrophages and proteinaceous material.

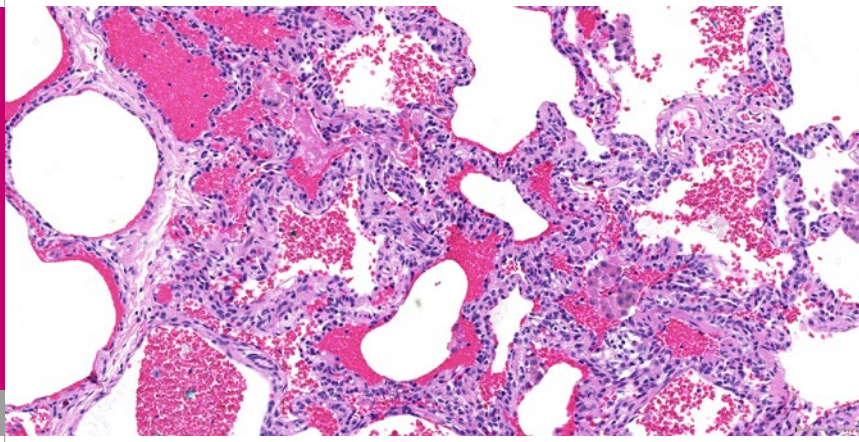

Fig. 7

Lung histology (200x, H&E stain) at 6 months: thickening of alveolar septae with mesenchymal cells and rare lymphocytes, enlarged airspaces, hyperplastic pneumocytes, intraalveolar hemorrhage with focal macrophages and proteinaceous material.

DISCUSSION

Childhood interstitial lung disease (chILD) is a heterogeneous group of rare conditions, which interfere with gas exchange and overall growth. The incidence is estimated between 0.13 and 16.2 cases per 1'000'000 children per year (1). In nearly 10% of cases, siblings are also affected (2). ChILD is more common in boys than girls (2).

Clinical presentation is non-specific. According to the American Thoracic Society (3), chILD should be suspected in any neonate or infant < 2 years of age with diffuse lung disease, in the absence of a more common disease, if at least 3 of the following 4 criteria are present: 1) respiratory symptoms like cough, rapid breathing and exercise intolerance, 2) clinical features like tachypnea, retractions, crepitations or crackles, 3) hypoxemia, and 4) abnormalities on chest X-ray or CT scan.

When suspecting chILD, patients should undergo structured diagnostic testing according to national and international consensus recommendations (3, 4). The first consists of a careful and comprehensive clinical evaluation (4). Despite being frequently abnormal, chest X-ray rarely leads to a specific diagnosis. High-resolution chest CT scan is the most important study as it confirms the presence of diffuse lung disease and in some cases may even allow a specific diagnosis (4). It also provides information about the extent and severity of the disease;

it is also helpful to choose the optimal site for lung biopsy (5).

Recommended laboratory investigations depend on the clinical presentation and age of onset of the disease. In infants, these may include genetic testing for surfactant protein dysfunction (SFTPB, SFTPC and ABCA3) or NKX2.1 mutations for brain-lung-thyroid syndrome in the presence of hypothyroidism and neurologic impairment (3). Underlying immunodeficiencies should be excluded, and metabolic testing to exclude lysosomal storage diseases and lysinuric protein intolerance are recommended. In older children, autoantibodies for connective tissue diseases and environmental organic dust exposure testing should be obtained to exclude hypersensitivity pneumonitis (4).

Bronchoscopy with bronchoalveolar lavage should be performed to rule out infection, pulmonary hemorrhage, structural airway abnormalities or recurrent aspiration (3). Echocardiography is necessary to exclude structural or functional heart disease or pulmonary arterial hypertension (3). Pulmonary function testing does not provide a diagnosis but is done in older children to delineate disease physiology and evaluate the severity of illness (2). When a specific diagnosis cannot be identified after all of these investigations, surgical lung biopsy is recommended (3).

The disorders associated with chILD in infants < 2

years of age are different from the interstitial lung diseases (DLD) affecting older children and adults (6). A specific classification based on clinical and pathological features was initially published by Deutsch et al. in 2007 (6), followed by more recent updates (3).

Chronic pneumonitis of infancy (CPI), first described in 1995 (7), occurs specifically in young children. This entity is defined by a typical histological pattern of marked alveolar septal thickening combined with uniform diffuse type II pneumocyte hyperplasia, macrophages and focal pulmonary alveolar proteinosis in the airspaces (7). This histological pattern can be present without a recognized genetic etiology, but in some reports (6, 8 – 10), CPI has been described in association with surfactant protein C (SFTPC) deficiency, inherited as an autosomal dominant disorder (11). For Deutsch et al., CPI is classified within the surfactant dysfunction disorders without a yet recognized genetic etiology nor with surfactant protein C mutations.

In our patient, analysis of SFTPC showed no pathogenic mutation or variant but two disease associated polymorphisms in a heterozygous state. These polymorphisms have been described in relation with respiratory distress syndrome and prematurity before 34 weeks of gestation; however, their significance in our patient with RDS and CPI should be interpreted with caution (12).

Treatment of chILD is mainly supportive with supplemental oxygen and nutritional support (13). The most frequent drugs used are systemic corticosteroids (14). Hydroxychloroquine, an anti-malarial drug, is also often used for its anti-inflammatory effects but the exact mechanism of action is unknown (4, 14). Macrolides, like azithromycin, represent another treatment option (4, 14). Treatment side effects must be monitored. The goal of treatment is to reduce inflammation in order to prevent pulmonary fibrosis. Thus far, there have been no controlled randomized trials of chILD treatments. Treatment decisions have to be made on a case-by-case basis and depend on the physician's experience. In our patient, preference was given to hydroxychloroquine rather than corticosteroids as there was little lung inflammation on biopsy and we were reluctant to submit this young child to long-term corticosteroid treatment.

The morbidity of chILD is high but varies between the different specific etiologies (1, 3). The overall mortality rates range from 6% to 30% (1). In CPI, the prognosis seems to be poor. In the initial series from Katzenstein published in 1995, 9 patients were described. Symptoms started between 2 weeks to 11 months of age and biopsies were performed between 9 days and 11 months after the onset of symptoms. Outcome is known for 6 of the 9 patients. Four of them were still alive 3 years after the biopsy. Out of the 4 survivors, 3 were treated with hydroxychloroquine and

corticosteroids but developed severe respiratory impairment leading to lung transplantation in one patient (7).

In 1998, Kavantzas reported 12 cases of CPI studied retrospectively on autopsy. Respiratory symptoms appeared between 1 to 9 months after birth. Seven patients were treated with corticosteroids and hydroxychloroquine. For the others 5 infants, the treatment is unknown. All died despite treatment before the age of five years (15). Fortunately, more recent case reports describe more favorable courses with adequate treatment (10).

CONCLUSION

ChILD is a heterogeneous group of rare conditions, which interfere with lung gas exchange and overall growth. ChILD should be suspected in any infant with chronic non-specific respiratory symptoms or failure to thrive, especially in the case of atypical late preterm or term RDS. Given the rarity of these disorders, steps to diagnosis and treatment are led by consensus and require a multidisciplinary approach.

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