


# Pulmonary surfactant metabolism dysfunction: A pediatric clinical case report

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## ABSTRACT

Interstitial lung diseases are rare in pediatrics. They include dysfunctions in the metabolism of pulmonary surfactant, an amphipathic molecule that reduces surface tension and prevents alveolar collapse.

Here we describe the case of a 6-month-old infant controlled for low weight, who presented with acute respiratory distress and cyanosis; his chest X-ray showed interstitial infiltrate, pneumomediastinum, and bilateral pneumothorax. During history-taking, it was noted that his mother had a history of hospitalization at 1 year old with unknown diagnosis, requiring prolonged oxygen therapy; she now shows signs of chronic hypoxia. The patient was hospitalized and required oxygen therapy. Ancillary tests were done to look for the etiology of the condition, with no positive results. A chest computed tomography showed ground-glass opacities, thickening of the septal interstitium, and areas of air trapping; based on the results of a lung biopsy and a genetic study, pulmonary surfactant metabolism dysfunction was diagnosed.

**Keywords:** *pulmonary surfactants; metabolism; interstitial lung disease.*

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## INTRODUCTION

Interstitial lung diseases (ILDs) are a group of rare conditions in pediatrics, which include disorders in the remodeling of the pulmonary interstitium and distal air spaces, resulting in an abnormal gas exchange.<sup>1,2</sup> In some ILDs, the primary pathology may occur outside the interstitium and, for this reason, some reference groups use the term “diffuse lung diseases” (DLDs).

The first classification system for ILD was developed for adult diffuse lung diseases, mainly based on their histology. Subsequently, a multidisciplinary approach developed better standardized terminology and diagnostic criteria. A United States group proposed the term chILD to refer to interstitial lung diseases of childhood and adolescence. These make up a heterogeneous group characterized by abnormal radiological findings and abnormal gas exchange, once common primary lung or extrapulmonary diseases have been ruled out. These include cystic fibrosis, immunodeficiency, heart disease, bronchopulmonary dysplasia, infections, primary ciliary dyskinesia, and recurrent aspiration.

There are no reliable estimates of childhood interstitial lung disease (chILD), but its prevalence is probably less than 1 in 100 000, compared with 60–80 in 100 000 in adults.

ChILD includes dysfunctions of pulmonary surfactant metabolism, also known as congenital surfactant protein deficiency.<sup>1</sup> This is a molecule that decreases surface tension and prevents alveolar collapse. It is composed mostly of phospholipids and 2–3% of specific proteins synthesized by type II pneumocytes, called A, B, C, and D.<sup>2</sup> Alterations in its composition result in different manifestations, from rapidly evolving severe conditions to slowly progressive, insidious onset scenarios.<sup>3</sup> This variety in clinical presentation is determined by the affected protein.<sup>4,5</sup>

The objective of this study is to describe the clinical case of a pediatric patient with pulmonary surfactant metabolism dysfunction.

## CASE REPORT

This was a male, 6-month-old infant born at term at 38 weeks of gestation with a low birth weight (2200 g) from a poorly controlled pregnancy exposed to perinatal syphilis. The infant was in outpatient follow-up due to his low weight with no other relevant personal history; he was taken to a local hospital for acute respiratory

distress, generalized cyanosis, and a single fever event. He was in poor general condition and had tachycardia, tachypnea, and poor respiratory mechanics. A chest X-ray showed pneumomediastinum, pneumothorax, and bilateral interstitial infiltrate, so he was referred to a tertiary care facility.

He was admitted to our hospital in poor general condition, with generalized chest retraction, tachycardia, tachypnea, and regular respiratory mechanics; therefore, high-flow nasal cannula (HFNC) therapy was indicated. The patient was hospitalized in the pediatric intensive care unit (PICU). In the first 24 hours, his clinical condition worsened, with increased respiratory distress and cyanosis and no response to non-invasive ventilation (NIV); for this reason, he was placed on mechanical ventilation (MV). A virological test of nasopharyngeal aspirate was negative; 2 blood cultures and a new chest X-ray were done, which showed bilateral interstitial infiltrate without signs of air leaks. Antibiotic therapy with ceftriaxone (10 days) was indicated. The patient was hospitalized with MV for 18 days, NIV for 24 days, and continued oxygen therapy with multiple unsuccessful attempts at weaning; he remained without developing any intercurrent disease and was clinically stable with marked tachypnea (50–60 breaths/min).

Several studies were done to establish the etiology: color Doppler echocardiogram (normal), screening for acid fast bacilli (AFB) in tracheal aspirate, determination of immunoglobulins (normal), Delta F508 mutation and alpha-1 antitrypsin, which were negative.

The patient's mother was found to have signs of chronic hypoxia (clubbing) (*Figure 1*) and a history of hospitalization at 1 year old with unknown diagnosis, requiring prolonged oxygen therapy, and with no other data worth noting during history taking.

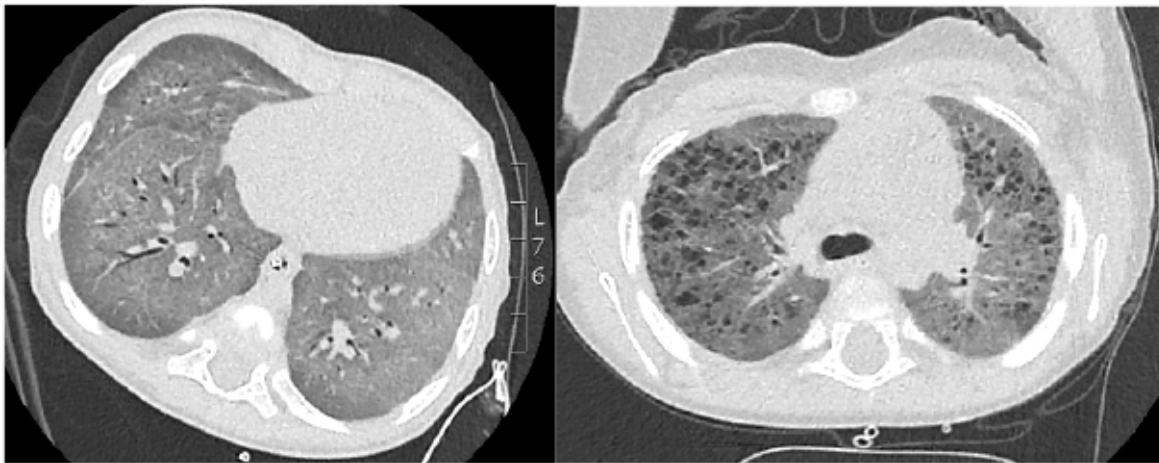
In view of the suspected diagnosis of interstitial lung disease, a high-resolution chest computed tomography was performed (*Figure 2*), which showed bilateral ground-glass opacities, thickening of the septal interstitium, and areas of air trapping. As part of an interdisciplinary approach, it was decided to perform a lung biopsy that reported distorted parenchymal tissue architectural structure with lobar remodeling, collapsing artifact defects, type II pneumocyte hyperplasia, and diffuse interstitial widening; these histological changes are compatible with dysfunction of pulmonary surfactant metabolism.

**FIGURE 1. Image of the mother's left hand**



*Drumstick fingers (clubbing) with rounded enlargement of distal phalanges.*

**FIGURE 2. Chest computed tomography**



*Bilateral ground-glass opacities distributed homogeneously, thickening of the septal interstitium, and areas of air trapping.*

After conducting the biopsy and once the pathological examination report was available, a genetic molecular study was performed which showed a likely pathogenic, heterozygous, autosomal dominant variant in the *SFTPC* gene (exon 3): c.218T>C p.(Ile73Thr) (PS3/PM2/PP3/pp4) that encodes the surfactant protein C.

During hospitalization, the patient received 3 pulses of methylprednisolone, with little clinical response, and remained with baseline tachypnea. After 3 months of hospitalization, he was counter-

referred to the local hospital to continue with hospitalization in the Pediatric Ward, requiring oxygen therapy via nasal cannula, while waiting for the provision of home oxygen therapy supplies.

#### **DISCUSSION**

Here we describe the case of a patient with surfactant protein C deficiency, a rare disease that requires a high index of suspicion for a timely diagnosis. Cardinal symptoms include cough, tachypnea, and growth retardation,

associated to a lesser extent with cyanosis and crepitant rales. This disease should be considered among the differential diagnoses in the study of patients with chronic hypoxemia, after other more frequent etiologies have been ruled out. Particularly, surfactant protein C deficiency manifests preferentially in the first months of life, although cases have been reported in older children or even in adults.<sup>3,4</sup> The clinical manifestations and the prognosis of surfactant metabolism dysfunction are determined by the affected protein.<sup>6,7</sup>

Currently, when faced with a patient with chronic respiratory disease, and having ruled out the most common conditions, it is necessary to suspect a group of diseases called diffuse lung diseases (DLDs), which include surfactant metabolism dysfunctions.<sup>8,9</sup>

In relation to ancillary tests, the observation of images with ground-glass pattern, predominantly in the lung bases, and thickening of the peripheral pulmonary interstitium is typical in high-resolution computed tomographies.<sup>10,11</sup> After doing less invasive studies, the next step would be a genetic study. Nowadays, genetic studies are more accessible and may help to establish a greater diagnostic certainty. It is done on peripheral blood samples; it involves purification of DNA, on which amplifications of different gene fragments are performed by polymerase chain reaction (PCR) techniques.<sup>12</sup> Once the genetic study results are available, an adequate family genetic counseling may be provided, since there are autosomal dominant and recessive forms. Sometimes diagnosis is not achieved with a genetic study or the disease progresses rapidly, and study results usually take 4 weeks, so, in these cases, a lung biopsy may be performed for histological analysis.<sup>13,14</sup> The most frequent findings are alveolar cell hyperplasia of type II pneumocytes associated with interstitial thickening and fibrosis.

In the case described here, protein C deficiency was diagnosed, a condition that usually presents a radiological pattern of interstitial involvement with onset in the first year of life and insidious course, which may benefit from corticosteroid and hydroxychloroquine use.<sup>15</sup>

Chronic respiratory diseases in childhood comprise a wide spectrum of conditions that vary in severity and involvement and may have a significant impact on children's quality of life and long-term pulmonary development. It is essential that pediatricians maintain a high level of clinical suspicion and consider the possibility of these

diseases in their differential diagnosis. Given the increased accessibility to genetic studies, health care providers are encouraged to consider this option prior to conducting invasive procedures, such as a lung biopsy.

In summary, childhood interstitial lung diseases encompass rare disorders, with diffuse infiltrates and alterations in gas exchange. Patients usually develop tachypnea, crepitant rales, and hypoxemia. A thorough examination is critical for an accurate diagnosis. It should be noted that, in contrast to invasive methods such as a lung biopsy, genetic studies offer a less invasive and safer alternative to obtain an accurate diagnosis. Consensus on the classification of chILD is required to support diagnosis and allow for evidence-based comparisons. Given its low incidence, it is necessary to establish local registries (in Latin America) of patients to advance in the understanding and management of these conditions. ■

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