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Congenital Pulmonary Alveolar Proteinosis: An Exceptional Cause of Diffuse Interstitial Lung Disease

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Abstract **Case Report**

Introduction: Pulmonary alveolar proteinosis is a rare respiratory disease characterized by the accumulation of surfactant-derived material in the lungs. It is commonly revealed by progressively increasing exertional dyspnoea contrasting with a poor clinical examination in the context of a diffuse infiltrating pneumonia. Bronchoalveolar lavage is the key to diagnosis. Genetic PAPs are usually diagnosed at birth or in childhood. PAPs of genetic origin mainly include surfactant production disorders, lysinuric protein intolerances and mutations of the GM-CSF receptor. CSF treatment is ineffective. On the other hand, large therapeutic lung lavage seems to be effective. The course of PAP is variable, ranging from spontaneous resolution to death from respiratory failure or lung infection. ***Case Report:*** A 3-month-old girl with family history of first-degree consanguineous parents, who was having a background of a Progressive worsening of respiratory symptoms and who was referred to our department for the treatment of diffuse pneumonia. The respiratory functional explorations objectified a restrictive syndrome. Chest X-ray revealed Bilateral alveolar-interstitial syndrome with left basal condensation and a Chest CT scan showed diffuse infiltrating pneumopathy, reasons why a bronchoalveolar lavage was performed showing a milky appearance. It contains a large amount of proteinaceous eosinophilic acellular granular material, which is PAS - positive. There are also foamy macrophages with PAS-positive intracellular inclusions. Those data are consistent with the diagnosis of PAP. The genetic study had shown an alpha chain mutation of the GM-CSF receptor confirming the diagnosis of primary alveolar proteinosis of genetic origin. The Evolution After two therapeutic bronchoalveolar lavages of both lungs was favorable with a clear decrease in pulmonary signs of effort. ***Conclusion:*** Alveolar proteinosis is a rare etiology of chronic interstitial lung disease in children. The diagnosis of certainty is done thanks to BAL and the treatment is based on therapeutic BAL sessions. The primitive forms are frequent and their prognosis seems be inversely correlated with age at onset.

Keywords: Pulmonary alveolar proteinosis, surfactant, congenital, GM-CSF receptor.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease first described by Rosen *et al.*, in 1958 [1]. It has also gone by several other names: alveolar proteinosis, alveolar lipoproteinosis, alveolar phospholipoproteinosis, and pulmonary lipidosis. PAP is characterized by the accumulation of surfactant-derived material in the lungs [2, 3]. This accumulation of PAS (periodic acid Schiff) positive eosinophilic material interferes with gas exchange. Classically, PAP is revealed by progressively increasing exertional dyspnoea contrasting with a poor clinical examination in the context of a diffuse infiltrating pneumonia (PID) assessment. Surfactant pathologies have long been represented by two very different clinical presentations. The first defining an extremely severe neonatal respiratory pathology leading to death in the first months of life. Surfactant protein B (SP-B) deficiency due to a homozygous mutation of the surfactant protein B gene (SFTPB) was the first cause isolated in 1993 [4]. The second picture is that of alveolar proteinosis characterized by an accumulation of surfactant in the alveolus in children and adults (secondary proteinosis) resulting in sometimes rapidly progressive respiratory failure. This already complex range of pathologies has been reinforced in the last ten years by the identification of mutations in the surfactant protein C gene (SFTPC) encoding surfactant protein C (SP-C) [5]. The main symptoms are nonspecific. Bronchoalveolar lavage is the key to diagnosis [6].

The course of PAP is variable, ranging from spontaneous resolution to death from respiratory failure or lung infection. In recent years, progress has been made in the classification, pathophysiology and therapeutic management of PAP, particularly in the event of failure of large therapeutic lung lavages (LTLL).

We present a new pediatric case of congenital alveolar proteinosis.

CASE REPORT

A 3-month-old girl was referred to our pediatrics department because of a productive cough complicated by respiratory discomfort, without associated extra-respiratory signs evolving for 7 days in a context of fever at 38-39°C. The patient was born at term with no immediate postnatal respiratory distress. She has a personal history of allergic rhino conjunctivitis and recurrent bronchiolitis. Her feeding with milk was mixed since birth with diversification at 6 months. The child is vaccinated according to the Moroccan national vaccination program: BCG, DTCP, HVB, MMR, and Pneumococcus. She had a good stature, weight and psychomotor development. No notions of pets, exposure to pollutants or taking medication. She has a family history of first-degree consanguineous parents and healthy 18-month-old brother. In the history of his illness, we find a Progressive worsening of respiratory symptoms (Exercise intolerance++, episodes of cyanosis, chronic cough, and frequent respiratory exacerbations), school absenteeism and a break in the height and weight curve since a year. Physical examination revealed a temperature at 38.8°C, Respiratory Rate at 38b/min, Heart Rate at 98 beats/min, SaO2 in ambient air at 96%, weight at 13Kg (-3 standard deviation), size at 109 cm (-1SD), crackles at the lung bases and a discreet digital clubbing. The liver and spleen were not enlarged.

Laboratory tests showed a PCR value at 172mg/l, white blood cell count at 13,000/mm3 (PNN at 3,290/mm3, LYM at 8,830/mm3), Hb level at 14.2g/l, platelet count at 296,000/mm3 and sedimentation rate at 17mm. otherwise, liver enzymes, renal function, were normal.

Phthysiological assessment was negative. Allergy and immune deficiency tests were negative. The assessment in search of a disease of the pulmonary localization system is negative. The respiratory functional explorations objectified a restrictive syndrome with a vital capacity of 62%, PCO2 at 38 mmHg, PH at 7.37 and Bicarbonate at 21.6 mmol/l. Chest X-ray revealed Bilateral alveolar-interstitial syndrome with left basal condensation (Figure 1). Chest CT scan showed diffuse infiltrating pneumopathy with a interstitial syndrome with “ground glass” opacities predominant in the periphery, the CT also showed a Thickening of the interlobular septa "crazy paving appearance" and a Bilateral condensation fireplaces (Figure 2). Echocardiography was normal. Respiratory fungal, viral, and bacterial pathogens were all negative. HIV testing was also negative. Because of a typical chest computed tomography and chest X-ray of a Diffuse Infiltrative Pneumonitis and after exclusion of metabolic or infectious causes, a bronchoalveolar lavage (BAL) was performed. Bronchial endoscopy is macroscopically normal. The bronchoalveolar lavage is "milky"(figure 3); it contains a large amount of proteinaceous eosinophilic acellular granular material, which is PAS - positive. There are also foamy macrophages with PAS-positive intracellular inclusions. Those data are consistent with the diagnosis of PAP. The genetic study had shown an alpha chain mutation of the GM-CSF receptor confirming the diagnosis of primary alveolar proteinosis of genetic origin. The patient received 3 sessions of therapeutic Broncho Alveolar Lavage (0, 1 month and 3 months apart), an anti-pneumococcal and anti-flu vaccination, antibiotic therapy based on Azithromycin (3 times a week) and protein supplementation based on Fortimel (2 vials per day). The Evolution After two therapeutic bronchoalveolar lavages of both lungs was favorable with a clear decrease in pulmonary signs of effort (dyspnea, cough, cyanosis), weight gain of 2.5 kg, improvement in the walking test, improvement in respiratory function (FEV 73% VS 62%) and radiological cleaning (figure 4). After nine bronchoalveolar lavages, there is a spectacular clinico-radiological improvement with a weight gain of 8 kg and a normal stress test.

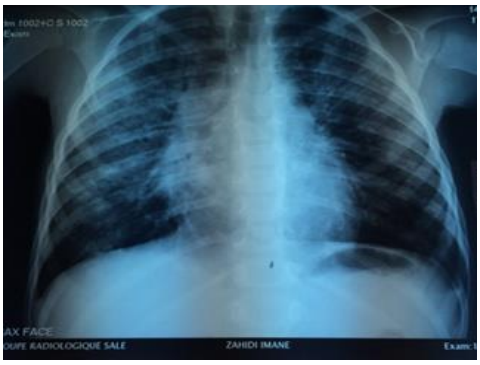


Figure 1: **Chest X-ray on admission showing Alveolo-interstitial syndrome bilateral with left basal condensation**

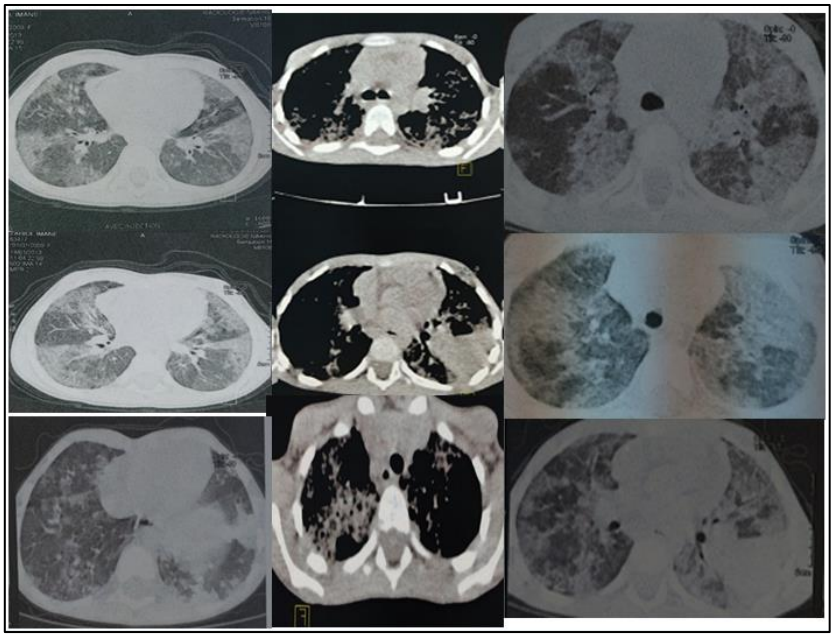
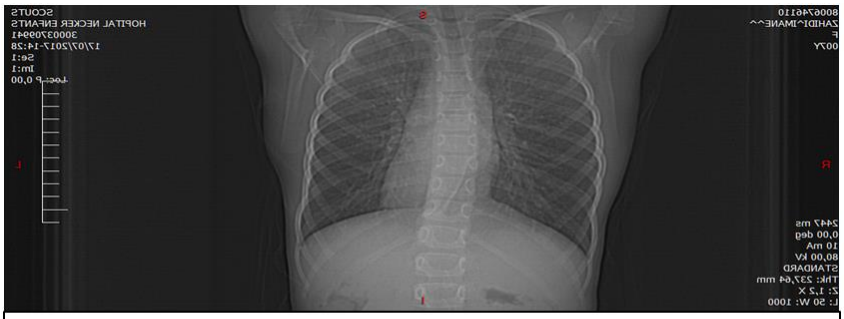
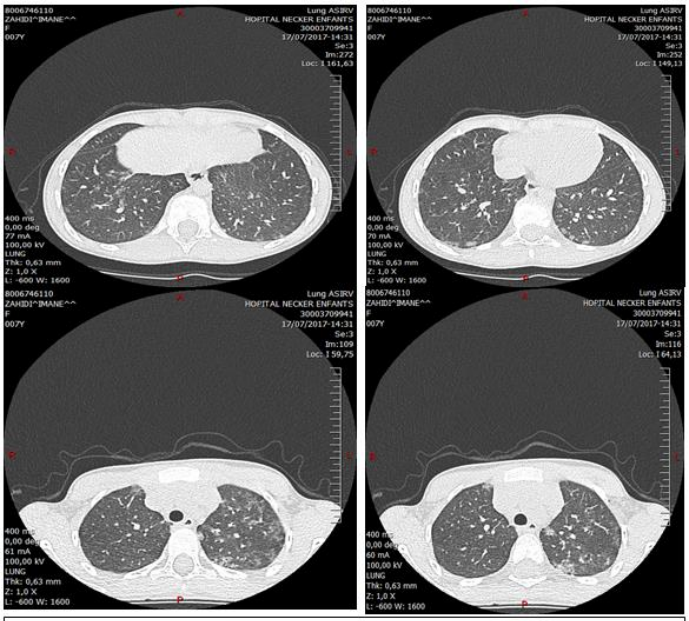


Figure 2: Chest CT scan on admission showing diffuse infiltrating pneumopathy with a interstitial syndrome with "ground glass" opacities predominant in the periphery; Thickening of the interlobular septa "crazy paving appearance" and a Bilateral condensation fireplaces

Figure 3: fluid taken from bronchoalveolar lavage for diagnostic purposes showing a milky appearance



A = Chest X-ray after two therapeutic bronchoalveolar lavages of both lungs



B= Chest CT scan after two therapeutic bronchoalveolar lavages of both lungs

Figure 4: morphological evaluation showing radiological cleaning

DISCUSSION

Surfactant is a thin lipid-protein film lining the alveolar epithelium and allowing the alveoli to not collapsing completely, even at the end of expiration, decreasing the surface tension of the air/alveolus interface [7].

GM-CSF (granulocyte-macrophage colony-stimulating factor) consisting of two subunits (GM-CSF-Ralpha and GM-CSF-Rbeta) due to its action on macrophages will play an essential role in the recycling of surfactant. Thus, it has been shown in experimental models that deletion of the gene coding for GM-CSF or for its receptor in mice caused an accumulation of surfactant in the alveoli [8-10].

PAP is rare in children, with only a few dozen cases reported in the literature [2]. PAP is characterized by the intra-alveolar accumulation of surfactant lipids and proteins impairing gas exchange and resulting in progressive respiratory insufficiency. Today, PAPs are classified into three groups:

- **Autoimmune PAPs:** characterized by the presence of anti-GM-CSF antibodies (granulocyte-macrophage colony-stimulating factor) serum, they represent 90% of all PAPs;
- **Secondary PAPs,** associated with:
  - Hematological diseases,
  - Toxic inhalations,
  - Infections;

- PAPs of genetic origin, which include:
  - Surfactant production disorders: with mutation surfactant protein B (SFTPB) genes, surfactant protein C (SFTPC), ATP-binding cassette 3 (ABCA3) and NK2 homeobox 1 (NKX2-1),
  - Mutations of the GM-CSF receptor,
  - Lysinuric protein intolerances,
  - Other mutations: GATA2 and telomerase complex.

Family history of a similarly affected sibling or consanguinity suggests autosomal recessive transmission [2]. In our case, infant had history of consanguineous parents. The later-onset form always appears after a postnatal, symptom- free period ranging from a few weeks to several years. The main symptoms are non-specific, including progressive-onset dyspnea during feeding or exercise and then at rest, cough, cyanosis, and digital clubbing. Asthenia and growth retardation are common. A clinical diagnosis of PAP can often be made by the characteristic milky colour of the bronchoalveolar lavage fluid, as is the case with our patient. Surgical lung biopsy, once considered like the gold standard, is no longer mandatory for diagnose PAP. A suggestive chest CT scan associated with a characteristic BAL should suffice to make the diagnosis in almost all cases. The surgical lung biopsy is no longer performed except in case of difficult diagnosis or one not previously mentioned.

The genetic study had shown an alpha chain mutation of the GM-CSF receptor confirming the diagnosis of primary alveolar proteinosis of genetic origin. Indeed, Genetic PAPs are usually diagnosed at birth or in childhood. PAPs of genetic origin mainly include surfactant production disorders, lysinuric protein intolerances and mutations of the GM- CSF receptor [11, 12], which is a heterodimer composed of

an alpha chain (CD116) which interacts with the ligand, encoded by the CSF2RA gene, and a beta chain (CD131), encoded by the gene CSF2RB, which is common to other cytokine receptors such as interleukin (IL)-3 or IL-5 [11, 13]. Mutations in the CSF2RB gene have been suspected in three patients presented with neonatal PAP and confirmed in two of them [11]. Gene Mutations CSF2RA has only been described in children. Inheritance is autosomal recessive, but penetrance is incomplete explaining the asymptomatic nature of a few patients. Clinical and radiological presentation is similar to autoimmune PAPs [13]. GM-CSF levels are elevated in the serum and bronchoalveolar lavage of these patients. GM-CSF treatment is ineffective. On the other hand, large therapeutic lung lavage seemS to be effective [13].

The progression of the disease is very variable, ranging from asymptomatic forms diagnosed with chance to early-onset forms that progress rapidly and result in uncontrollable respiratory failure [14].

In our case, Whole lung lavage has been widely used as a treatment and has been associated with long-term survival. Short and long term evolution is favorable with spectacular clinico-radiological improvement.

CONCLUSION

Alveolar proteinosis is a rare etiology of chronic interstitial lung disease in children. The diagnosis of certainty is done thanks to BAL and the treatment is based on therapeutic BAL sessions. The primitive forms are frequent and their prognosis seems be inversely correlated with age at onset.

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