Hereditary pulmonary alveolar proteinosis. Could it be triggered by *Mycoplasma pneumoniae* pneumonia?

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Summary
We present a three-year-old girl with respiratory failure due to hereditary pulmonary alveolar proteinosis caused by abnormal alpha chain of the granulocyte-macrophage colony-stimulating factor receptor. Both the patient and an asymptomatic seven-year-old sister were homozygous...
Introduction

Hereditary pulmonary alveolar proteinosis (PAP) is caused by abnormalities in either the alpha or the beta chains of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor due to mutations in their genes (CSF2RA and CSF2RB). Defective GM-CSF signaling causes failure in surfactant clearance by alveolar macrophages leading to alveolar accumulation of surfactant lipids and proteins.¹ So far only 13 patients have been reported 5 of them with beta chain abnormalities,²⁻⁴ including two asymptomatic siblings and one adult onset case.³ It has been speculated that the great variability in the clinical presentation may be due to additional factors altering surfactant homeostasis and so triggering the clinical onset and/or its severity.¹,² Whole-lung lavage (WLL) remains the preferred therapy.² As this technique has limitations in young children with small airways alternative methods such as partial-lung lavage (PLL) have been developed.⁵⁻⁷ We report a 3-year-old girl with hereditary PAP caused by abnormal alpha chain of the GM-CSF receptor associated with Mycoplasma pneumoniae pneumonia, with a good response to serial PLL. Investigation of several family members disclosed that both the patient and an older asymptomatic sister shared the same genetic and molecular abnormalities.

A case report

Three-year-old girl, the youngest of three female siblings born from consanguineous (first cousins) parents of Moroccan ancestry. Her personal and familial history were otherwise uneventful, and she had had normal growth with weight and height the 35th and 75th percentiles. She presented in September 2010 with six day fever, coughing, nasal discharge and hypoxemia (TcSaO₂ 93% breathing room air). She required oxygen supply 1–3 l/min. Her weight had dropped to the 10th percentile, but her general condition was otherwise good. Her temperature was 37.2°C, she was pale, and had mild bilateral decreased breath sounds on chest examination. A chest CT-scan showed a striking bilateral "crazy-paving" pattern (Fig. 1c). On BAL a milky liquid (Fig. 1d) with granular proteinaceous periodic acid-Schiff (PAS) positive material was recovered, supporting the diagnosis of PAP which was confirmed by surgical pulmonary biopsy (Fig. 1e and f).

Table 1 shows a summary of the clinical progress. Molecular genetics investigation was done in the “Rare Lung Disease Network”, Cincinatti Children’s Hospital Medical Center (Dr. B.Trapnell) once informed consent was obtained. It showed blood leukocyte abnormalities suggesting defective GM-CSF receptor: no GM-CSF dependent phosphorylation of STAT5, increased serum GM-CSF concentration (73.66 pg/ml), undetectable GM-CSF receptor alpha-chain. The patient was found be homozygous for two mutations in the CSF2RA: c.50C > G (p.Ala17Gly) in exon 3, and c.586G > C (p.Gly196Arg) in exon 7. GM-CSF autoantibody testing was negative.

She underwent PLL in December 2010 and March 2011 with a 1-week interval between the right and left lung lavages. An Olympus 3.6 mm bronchoscope was passed through a 5.5 mm endotracheal tube at the theater and 20 ml 0.9% warm saline aliquots were flushed into every pulmonary segment, until the recovered fluid was clear. The first procedure could not be completed as the patient developed severe hypoxemia. The aliquots volume was decreased to 15 ml and the remaining procedures were well tolerated. The total infused volume at the procedures ranged from 150 to 250 ml, 50%—75% being recovered. They lasted for about 2 h and the patient required oxygen supply for 24 h with clear improvement subsequently. The outcome of all the procedures was similar. She was asymptomatic 3 weeks after the last lavage with TcSaO₂ 98% breathing room air, and her chest-ray changes had improved.

The investigation of the family showed that the parents and one of the patient’s sisters were heterozygous for both mutations, the STAT5 phosphorylation index was normal and GM-CSF receptor alpha and beta proteins were detected. The other sister aged 7 years was also found to be homozygous for both mutations (Fig. 2). GM-CSF dependent STAT5 phosphorylation and the GM-CSF receptor alpha-chain were undetectable. However she had had not significant symptoms, her physical examination was unremarkable and her TcSaO₂ was 98% on room air. We agreed with the parents to keep her under regular follow-up postponing further investigations as long as she remained symptom-free.

Hereditary pulmonary alveolar proteinosis

Mycoplasma pneumoniae; Partial lung lavage

for the same mutation in CSF2RA. We speculate that the Mycoplasma pneumoniae pneumonia might have triggered the clinical presentation. While a good response to serial partial lung lavage was noticed, the ultimate outcome is uncertain. © 2012 Elsevier Ltd. All rights reserved.
This study was approved for its publication by the Clinical Research and Ethics Committee at Cruces Hospital University.

**Discussión**

PAP is mostly an autoimmune condition in children, hereditary cases being less than 6%.\(^2\) Alveolar structure is maintained in the latter, unlike surfactant production disorders, and they mimic the autoimmune-mediated cases both in clinical presentation and their good response to pulmonary lavage.\(^3\) Genetic cases are transmitted as an autosomal recessive trait, by several disease-causing mutations with variable penetrance. The diagnosis of the disease in our symptomatic case prompted the finding of the same mutations in her asymptomatic sister, both being homozygous for pAla117Gly and pGly196Arg. The latter has been previously reported in two siblings with PAP, and the abnormality of the CSF2RA was reproduced in vitro studies. The mutation alters one of the potential sites of N-glycosilation required for GM-CSF receptor activation.\(^9\)

In symptomatic cases of hereditary PAP the onset the symptoms often occurs 1–2 years before the diagnosis is suspected, and failure to thrive is common.\(^2\) The previous "silent" period may range from weeks to years, and it has been speculated that its duration may depend on the

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**Figure 1** Pulmonary alveolar proteinosis (PAP) diagnosis. (a) Chest X-ray demonstrating right upper lobe consolidation with a bilateral interstitial pattern, and (b) bilateral reticulonodular pattern. (c) Sagittal CT-scan showing a "crazy-paving" pattern. (d) Milky-looking liquid recovered at BAL. (e) Alveoli full of granular eosinophilic PAS + material (optic microscope). No interstitial involvement. (f) Lamellar bodies (electronic microscope).
extent of preserved macrophage function by receptor intact chain-mediated signaling and/or factors other than GM-CSF. Other hitherto undefined agents altering surfactant homeostasis could contribute to the wide clinical spectrum of the disease. The clinical presentation in our patient was abrupt and was associated with M. pneumoniae pneumonia. Macroscopic and microscopic appearance of the first BAL was not suggestive of PAP. The older sister sharing the same molecular-genetic pattern remained completely asymptomatic and while she was not tested for M. pneumoniae it is unlikely she was infected.

Infection often occurs in PAP, being difficult to ascertain whether it works as a trigger or is a mere complication of the disease. Cases following Cytomegalovirus, Mycobacterium tuberculosis, Nocardia spp, Pneumocystis jiroveci have been reported, and in some either quantitative or functional macrophage deficiency have been found. In another case following Epstein Barr virus infection autoantibodies to GM-CSF were present. M. pneumoniae infection may disrupt surfactant homeostasis by a number of pathways (intraalveolar fibrin accumulation, type 2 pneumocytes hyperplasia, and defective surfactant composition and function), thus we speculate the M. pneumoniae infection may have triggered the onset of the clinical symptoms.

PLL has been proposed as an alternative to WLL especially in young children in whom the latter is often technically difficult or impossible. Hypoxia and hemodynamic instability are common probably due to loss of surfactant activity, in lavaged and neighboring areas subject to leaks of the inflowed saline. We lavaged the most affected segments occluding them at the end of the bronchoscope while the remaining lung was ventilated. Hypoxia correlated with the aliquot volumes and resolved when we cut them down.

The ultimate prognosis of the disease is uncertain. In the only published study on 8 children with CSF2RA mutations most symptomatic cases still required oxygen with a 1–3 year follow-up, one had died, and one was symptom-free. Our patient required two PLL over six months with good clinical response, becoming asymptomatic and not requiring oxygen although chest X-rays remained abnormal. Our patient’s sister remained symptom-free despite her molecular-genetics pattern suggested mild or subclinical PAP, similarly to other two reported cases who remained asymptomatic with a 3 years and 9 months follow-up. Careful monitoring of patients at risk to develop clinical PAP could help ascertain those factors conditioning the onset and/or the severity of the disease.

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Conflict of interest statement

The authors declare no conflict of interest.
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