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

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KEYWORDS
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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

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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.

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.[5] 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.[6–8] 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). All remaining family members were symptom-free. A chest X-ray showed right upper lobe (RUL) consolidation and a bilateral interstitial pattern (Fig. 1a). WBC was 17,600 (70% PMNs, 20% lymphocytes, 8.6% monocytes, 1% eosinophils, 0.2% basophils). Serum C Reactive Protein 13.1 mg/dl. Serum antibodies to *Chlamydia*, *Coxiella* and *M. pneumoniae* were all negative. Total serum antibody *M. pneumoniae* was below 1/80 (SERODIA-MYCO II, Japan). She was administered oral azithromycin and received oxygen supply for three days and was discharged 5 days after admission. Three weeks later clinical worsening with increasing cough, breathlessness and hypoxemia (TcSaO293% on room air) were noted. A chest X-ray showed a bilateral reticulonodular pattern without RUL consolidation (Fig. 1b). She was treated with antibiotics and antituberculosis drugs until work-up for *Mycobacteria* proved to be negative. On bronchoalveolar lavage (BAL) a serum-like liquid with abundant macrophages and scarce neutrophils was recovered. Serum antibody titer to *M. pneumoniae* was positive (equal or higher than 1/1280). In November 2010 she was admitted again with polypnea 64/min, breathlessness on mild exertion and severe hypoxemia (TcSaO2 82%—85% on 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°, 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 pcg/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.