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Case report

Pulmonary alveolar proteinosis and Niemann Pick disease type B: An unexpected combination

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ABSTRACT

Background: Pulmonary involvement in Niemann-Pick disease (NPD) is a common finding, especially in type B. It usually manifests with symptoms of restrictive lung disease appearing in adulthood but showing gradual deterioration over time. Treatment options have been dramatically limited, with whole lung lavage offering only temporary improvement. Pulmonary alveolar proteinosis (PAP) has been previously mentioned as part of lung disease in NPD, but only in rare cases of type C2. This is the first study that reports the coexistence of autoimmune PAP with NPD type B.

Case presentation: An 8 year old female patient with the diagnosis of NPD type B and a 2-year history of respiratory symptoms, presented with another episode of severe respiratory distress. Chest imaging revealed a “crazy paving pattern”, raising concern for PAP. After admission to the intensive care unit and application of non-invasive positive pressure ventilation, a whole lung lavage was performed with return of a milky-appearing proteinaceous fluid. Her status post-lavage was markedly improved, while genetic testing placed the diagnosis of autoimmune PAP. The patient was initiated on inhaled GM-CSF treatment and shows a beneficial outcome to date.

Conclusions: In spite of the patient's symptoms being consistent with NPD type of lung involvement, clinical findings raised the suspicion of an underlying disorder, which surprisingly proved to be PAP. The detection of anti-GM-CSF autoantibodies in our patient allowed the initiation of inhaled GM-CSF treatment, which is likely to prove more beneficial in her prognosis than repeated lung lavages.

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1. Background

Niemann-Pick disease (NPD) is a heterogeneous group of lysosomal storage disorders inherited in an autosomal recessive manner. In types A and B the affected gene is SMPD1, which codes for the enzyme acid sphingomyelinase (ASM) [1]. Deficiency of this enzyme causes sphingomyelin to accumulate within lysosomes of macrophages, causing mainly hepatosplenomegaly. The prevalence of ASM deficiency in the population is estimated to be 1/300,000 [2]. NPD type A is characterized by a severe neurological deterioration causing death in all patients within the first 3 years of life. NPD type B can present later in life with predominantly visceral symptoms, and has a more favorable prognosis, with patients

surviving into adulthood. NPD type C is caused by a mutation in the genes NPC1 or 2, affecting the intracellular transport of cholesterol. It is defined by its progressive neurodegenerative nature which becomes fatal usually in adolescence [3].

Presence of pulmonary involvement in Niemann-Pick disease has been well described in various case reports. Type B is the type most commonly associated with respiratory compromise, mainly expressed through interstitial lung disease [4]. Symptoms of dyspnea and exercise intolerance become mostly apparent in adulthood. No effective treatment has been discovered other than lung lavage which temporarily improves lung function [5]. However, the disease progressively deteriorates, accounting for the mortality of some patients of this type [6].

Pulmonary Alveolar Proteinosis (PAP) is an extremely rare disease. It is classified as autoimmune, hereditary, secondary and idiopathic [7]. The autoimmune or acquired form accounts for 98% of cases and is caused by the presence of anti-GM-CSF antibodies. These autoantibodies suppress the production and effectiveness of

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macrophages, which normally remove the excess surfactant from the alveoli, leading to the buildup of substantial amounts of surfactant within the distal airways. Moreover, the immune response wanes, leading to recurrent infections. On the other hand, hereditary or congenital alveolar proteinosis occurs as a result of mutations in genes affecting surfactant metabolism (genes SFTPB, SFTPC, ABCA3, NKX.2), cationic amino acid membrane transport (gene SCF7A7), or the beta chain of the GM-CSF receptor (genes CSF2RA and CSF2RB). Secondary forms of PAP can be provoked by a variety of diseases including infections, hematological malignancies, immune deficiencies and inhaled irritants or chemicals.

The coexistence of NPD with PAP has been mentioned in several studies, but only concerning the type C of the disease. In particular, PAP has always been described as part of the respiratory outcome of the disease, especially the type 2C, contributing to its mortality [8,9]. We hereby present a rare and previously undescribed pulmonary presentation of a pediatric patient with NPD type B and PAP.

2. Case presentation

L.A. is a female patient of Saudi Arabian descent, born in 2006 from parents that were first-degree relatives. She was the product of an uncomplicated pregnancy. Her birth weight was 3,000 g, and early milestones were met at the appropriate time. Her symptoms began at the age of 9 months with abdominal distension and hepatosplenomegaly, but no specific diagnosis was made at that time. At the age of 6 years, pulmonary symptoms began, with worsening respiratory distress, cyanosis, clubbing and poor exercise tolerance, requiring multiple ICU admissions. The patient eventually became dependent on supplemental oxygen, requiring up to 7Lpm of oxygen daily, with rapid oxyhemoglobin desaturation with activity. In addition to the persistent hepatosplenomegaly, she developed thrombocytopenia, with easy bruising and epistaxis. Her weight and height ranged below the 3rd percentile, but she never showed any neurological symptoms. A genetic study was performed and identified homozygous mutations in SMPD1 gene (c.C947A), confirming the diagnosis of NPD type B. However, due to her significant visceral and pulmonary involvement she was not considered a candidate for a hematopoietic stem cell transplant (HSCT). Her younger sister also carries the exact same mutation, but her significantly milder pulmonary symptoms rendered her suitable for HSCT.

At the age of 8 years L.A. was referred to the Children's Hospital of Philadelphia for further evaluation. At the time of presentation she appeared in severe respiratory distress and was acutely admitted to the ICU, where non-invasive positive pressure ventilation was applied due to her impending respiratory failure. CT scan of the chest showed a diffuse "crazy paving" pattern, raising concern for PAP (Fig. 1A). A bilateral whole lung lavage (WLL) was subsequently performed with return of a milky-appearing fluid consisting of abundant granular PAS-positive proteinaceous material strongly suggestive of PAP. Her clinical and radiological status post whole lung lavage was extremely ameliorated, requiring only ½ Lpm nocturnal supplemental oxygen (Fig. 1B). Meanwhile, genetic testing results identified the presence of serum GM-CSF autoantibodies and an abnormal STAT5 phosphorylation index test, confirming the diagnosis of autoimmune PAP. No mutations in genes SFTPB, SFTPC, ABCA3, NKX.2, and no decrease in GM-CSF receptors on the surface of leukocytes were identified, excluding congenital PAP. Inhaled GM-CSF was then initiated and continued on a daily basis. Follow-up visits for clinical evaluation and chest x-ray were initially arranged every 2 months or sooner in case of a decompensation in her respiratory status. After 6 months of therapy, GM-CSF effect has been proved beneficial with her exercise tolerance being drastically improved, yet she continues to require only 1/2LPM supplemental oxygen with sleep.

3. Conclusions

NPD type B has frequently been associated with respiratory involvement. It usually consists of progressive deterioration of pulmonary function, which most commonly manifests in adult life and is very rarely the presenting symptom of the disease [3]. Patients may be initially asymptomatic and their respiratory disease may be incidentally detected. When symptomatic, patients present with mild-to-moderate dry cough and exercise intolerance, suggesting interstitial lung disease [10]. The process of decline is gradual, with patients eventually developing recurrent respiratory infections and chronic respiratory failure [11]; however, there have been described rare cases of rapidly progressive lung disease [10].

Radiological evidence of lung disease consists of diffuse thickening of the interlobular septa suggesting mild interstitial fibrosis, along with ground glass opacities caused by the endogenous lipoid pneumonia [12]. These two features form what is known as a "crazy-paving" pattern, highly non-specific for the disease. Other

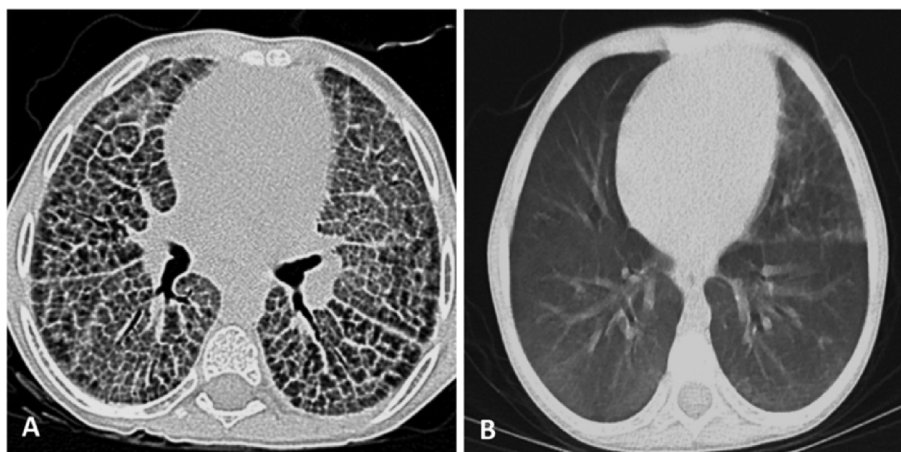


Fig. 1. High resolution CT scan of the chest pre- (A) and post- (B) whole lung lavage. (A) At the initial presentation of the patient, diffuse "crazy-paving" pattern was observed, consisting of scattered ground-glass opacities with superimposed thickened interlobular septa. Heart size is normal. No pneumothorax, pneumomediastinum or pleural effusion is seen. (B) After whole lung lavage was performed, there is marked improvement of the previously mentioned opacities, with only a few septal thickenings and ground glass opacities remaining.

imaging findings described include nodules, cysts or even lobar emphysema [13,14]. It has been noticed though that the imaging extent of disease does not correlate with its severity [15].

Treatment options of NPD are dramatically limited. HSCT can potentially alleviate some of the visceral symptoms, especially if performed early in life [16]. However there is still limited experience and possibly severe hepatic and neurological adverse effects [17]. Recombinant sphingomyelinase therapy is still under research and therefore it is not clinically available [18].

In cases of pulmonary involvement, bilateral or unilateral lung lavage causes temporary improvement of respiratory function, but does not alter the progress of the disease [19]. The fluid drawn from lavage also aids in the diagnosis of the disease, as it consists mainly of foamy macrophages and possibly inflammatory cells [10]. Foamy macrophages are highly suggestive but not specific for NPD.

The connection of PAP with Niemann-Pick disease has always been that PAP occurs secondarily to the underlying metabolic disease [20]. However, in the case we described, the presence of GM-CSF autoantibodies validated the autoimmune nature of PAP, which completely alters the management and possibly the prognosis of the patient. Inhaled GM-CSF has been proved to alter the course of the disease in 80% of PAP patients and can be safely administered in moderate-to-severe cases of autoimmune PAP [7,21]. Novel therapies, such as transplantation of macrophage progenitors are under investigation and have shown early positive results [22].

Had the patient's pulmonary symptomatology been considered secondary to her underlying metabolic dysfunction, the treatment options would not be other than repeated lung lavage when needed based on the patient's status. The discovery of the autoimmune aspect enabled the addition of a targeted therapy that can significantly alter the course of present respiratory dysfunction.

The present study intends to present yet another manifestation of a patient with NPD type B. It also means to highlight that upon suspicion of PAP in a patient with underlying disorders, physicians must always exclude the presence of GM-CSF autoantibodies, in order to offer the patient an efficient targeted therapy and a more tailored management.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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List of abbreviations

ASM	Acid sphingomyelinase
GM-CSF	Granulocyte macrophage colony-stimulating factor
HSCT	Hematopoietic stem cell transplant
NPD	Niemann-Pick Disease
PAP	Pulmonary alveolar proteinosis
WLL	Whole lung lavage

Competing interests

The authors declare that they have no competing interests.

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