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

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1. Background

Niemann-Pick disease (NPD) is a heterogenous 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
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, SFTP C, 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 up to 7 Lpm of oxygen daily, with rapid oxyhemoglobin desaturation. The patient eventually became dependent on supplemental oxygen, requiring up to 7 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 1/2 LPM 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
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

| Acronym | Definition |
|---------|------------|
| 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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