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# Combined Emphysema and Interstitial Lung Disease as a Rare Presentation of Pulmonary Involvement in a Patient with Chronic Visceral Acid Sphingomyelinase Deficiency (Niemann-Pick Disease Type B)

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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Literature Search F  
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**Conflict of interest:** None declared

**Patient:** Male, 45-year-old  
**Final Diagnosis:** Niemann-Pick disease type B  
**Symptoms:** Hepatosplenomegaly • lung fibrosis  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Pulmonology

**Objective:** Rare disease

**Background:** Niemann-Pick disease is a rare genetic disorder caused by mutations in sphingomyelin phosphodiesterase 1 gene. It results in acid sphingomyelinase deficiency (ASMD) and sphingomyelin intracellular accumulation. Lung disease is diagnosed mostly in chronic visceral ASMD. Ground-glass opacities and smooth interlobular septal thickening are described most frequently. They are localized predominantly in the lower parts of both lungs.

**Case Report:** The authors describe a rare type of lung involvement, composed of emphysema and interstitial lung disease (ILD), in a nonsmoking adult male with chronic visceral ASMD. Areas of ground-glass opacities and lung fibrosis presenting as reticulation and bronchiectasis have been described in high-resolution computed tomography of the lungs. The radiological findings were localized predominantly in the middle and lower parts of both lungs. Large air spaces of marginal emphysema, localized in the upper lobes, were also demonstrated. Foamy macrophages, staining blue with May-Grünwald-Giemsa, were found in bronchoalveolar lavage, confirming lung involvement in the course of ASMD. The course of disease was stable, with no hypoxemia at rest. Nevertheless, because of markedly decreased lung transfer for carbon monoxide and significant desaturation on exertion, further controls have been planned, with qualification for long-term oxygen therapy in case of deterioration.

**Conclusions:** We present a unique type of lung involvement, combined emphysema and ILD, in a nonsmoking adult patient with chronic visceral ASMD. On such occasion chronic obstructive pulmonary disease coexisting with ILD as well as chronic pulmonary fibrosis and emphysema syndrome should be excluded.

**MeSH Keywords:** Lung Diseases, Interstitial • Niemann-Pick Diseases • Pulmonary Emphysema

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## Background

Niemann-Pick disease (NPD) is a rare autosomal recessive disorder caused by mutations in the sphingomyelin phosphodiesterase 1 gene (*SMPD1*), which is responsible for acid sphingomyelinase activity. Subsequent acid sphingomyelinase deficiency (ASMD) and sphingomyelin intracellular accumulation are observed [1].

The incidence rate is 0.4–1/100 000 newborns [2,3]; a higher prevalence may be noted in selected populations of carriers [4]. Three types of disease have been described. Type A, called infantile neurovisceral ASMD, is usually lethal. Type A/B, called chronic neurovisceral variant, may result in longer survival. Type B (chronic visceral ASMD) usually presents as a slowly progressing, less severe disease, with little or no neurological deficits, and better prognosis [2,5,6].

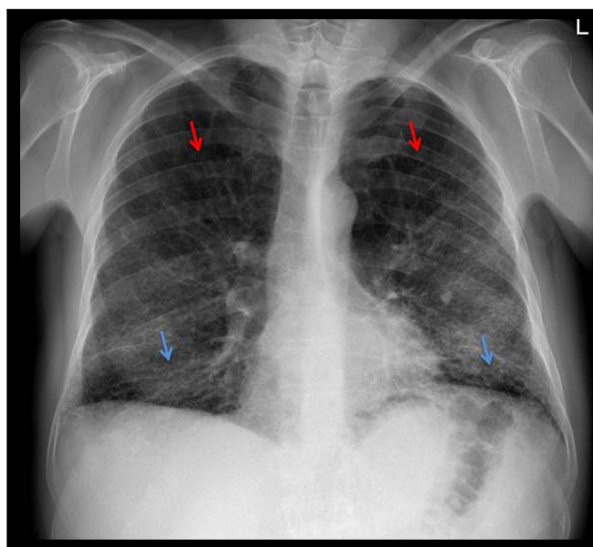
Pulmonary involvement is seen in all types of NPD, most frequently in chronic visceral ASMD [3]. Typically it presents as interstitial lung disease (ILD) characterized with bilateral ground-glass opacities, smooth interlobular septal thickening, and occasionally centrilobular nodular opacities localized predominantly in lower parts of the lungs [3]. Lung emphysema combined with ILD seems to be a very rare presentation of chronic visceral ASMD. Therefore the aim of the present study was to describe a rare radiologic presentation of chronic visceral ASMD, combined emphysema and ILD.

## Case Report

A 64-year-old Polish male of Caucasian ethnicity was diagnosed with chronic visceral ASMD in 1994 at the age of 45 years on the basis of mutation c.1400A>C;p.Tyr 467Ser/c.996delC;pF333Sf\*52 found in *SMPD1* and ASMD in fibroblasts 1.5;1.8 mkat/kg of cell protein (normal=30±10).

Recurrent respiratory infections as well as splenomegaly have been observed since childhood. He was also diagnosed with arterial hypertension and hypothyroidism. The patient has been a lifelong nonsmoker, with no significant exposure to passive smoking, toxic gases, or other substances. The family history was negative for ASMD.

The patient was admitted to the Department of Lung Diseases because of dyspnea on exertion increasing from June 2017, and radiological signs of parenchymal lung disease. On admission, he was in good performance status, with no dyspnea at rest. Physical examination revealed inspiratory crackles over both lung bases and hepatosplenomegaly.

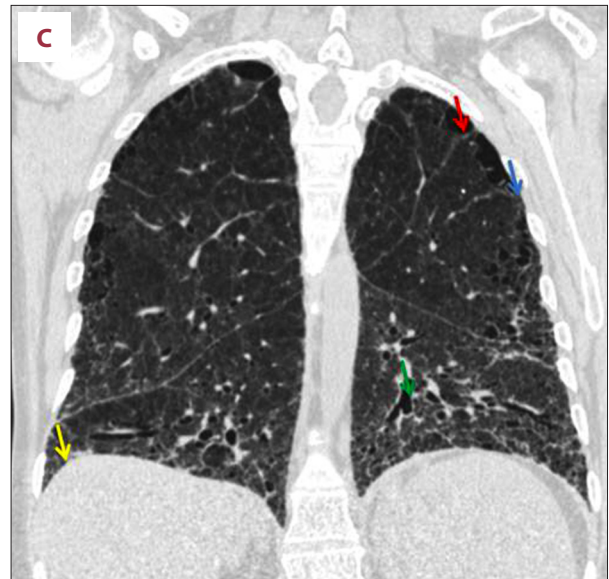
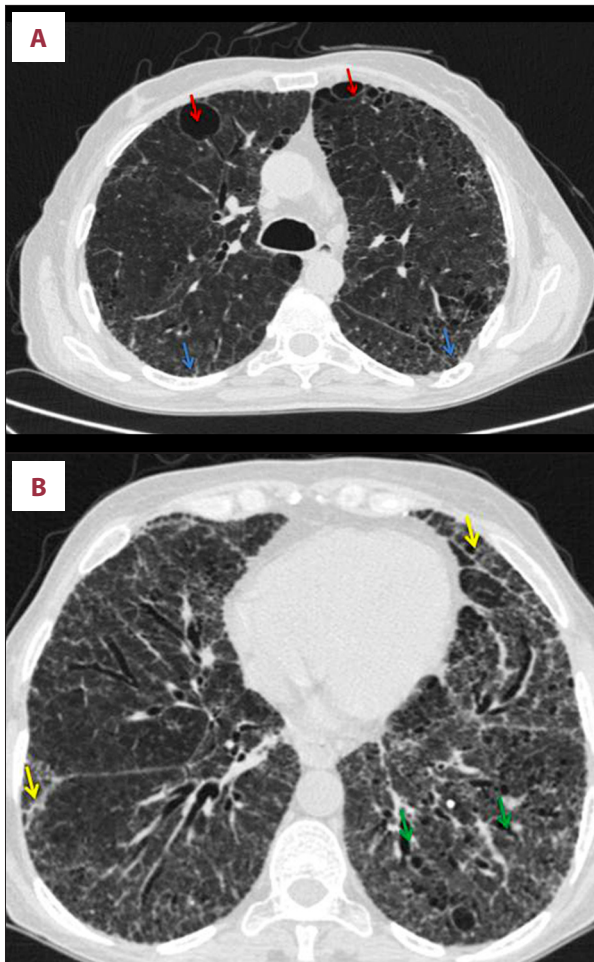


**Figure 1.** Chest radiograph, with posteroanterior projection. Diffuse reticular pattern seen predominantly in the lower fields (blue arrows). Upper lobes predominant emphysema (red arrows).

Oxygen saturation was 96%, PaO<sub>2</sub> 76 mmHg, PaCO<sub>2</sub> 32 mmHg, pH 7.43, erythrocyte sedimentation rate 52/h. Blood morphology revealed thrombocytopenia at 97×10<sup>9</sup>/L; lipid profile was increased triglycerides 227 mg/dl (normal <50 mg/dl) and decreased high-density lipoprotein fraction of cholesterol 14 mg/dl (normal >40 mg/dl). Antinuclear antibody titer was 1: 320; no specific autoantibodies have been found. Rheumatoid factor was 16 IU/ml (normal <14 IU/ml).

Chest X-rays showed reticular opacities localized in both lower parts of the lungs and emphysema predominantly in the upper lobes (Figure 1). High-resolution computed tomography of the lungs (HRCT) revealed ground-glass attenuations and lung fibrosis presenting as reticulation and bronchiectasis, localized in the middle and basal parts of both lungs. Honeycombing was not present. Upper lobes with predominant, paraseptal emphysema with areas of interlobular septal thickening was also described (Figures 2A–2C, 3).

During a 6-min walking test, the patient covered a distance of 540 m, with initial and end-walking saturation of 96% and 90%, respectively. Lung volumes were within normal limits, with no signs of restriction or obstruction: total lung capacity (TLC) 5.57 L (99% of predicted), forced vital capacity (FVC) 3.83 L (100% of predicted), forced expiratory volume in 1 s (FEV<sub>1</sub>) 3.13 L (105% of predicted), FEV<sub>1</sub>%FVC 82%, residual volume (RV) 1.74 L (74% of predicted), RV/TLC 80% of predicted. Nevertheless, marked decrease of transfer factor for carbon monoxide (T<sub>l,CO</sub>) has been noted: 3.26 mmol/min per kPa (39% of predicted).



**Figure 2.** (A) High-resolution computed tomography (HRCT) of the lungs, axial plane. Paraseptal emphysema (red arrows) with interlobular septal thickening (blue arrows) predominantly in the upper lobes. (B) HRCT, axial plane. Areas of ground-glass opacities and lung fibrosis with reticulation (yellow arrows) and bronchiectasis (green arrows) predominantly in the middle and lower parts of both lungs. (C) HRCT, coronal reconstruction paraseptal emphysema (red arrow) with interlobular septal thickening (blue arrow) predominantly in the upper lobes. Areas of ground-glass opacities and lung fibrosis with reticulation (yellow arrow) and bronchiectasis (green arrow) predominantly in the middle and lower parts of both lungs. No mediastinal or hilar lymphadenopathies are observed.

Echocardiography revealed pulmonary hypertension: tricuspid valve peak gradient 46 mmHg, right ventricular to pulmonary artery outflow acceleration time (Act) 75 ms, with normal left ventricular ejection fraction 64% and no signs of right ventricular strain. Serum N-terminal brain natriuretic propeptide was within normal limits (104 pg/ml).

Bronchoalveolar lavage (BAL) documented increased number of cells:  $42 \times 10^6$ , with normal cell subpopulations: 92.7% macrophages, 5.6% lymphocytes, 1.5% neutrophils, 0.2% eosinophils. Large multivacuolated macrophages were present (foamy macrophages), staining blue with May-Grünwald-Giemsa (MGG) method (Figure 4).

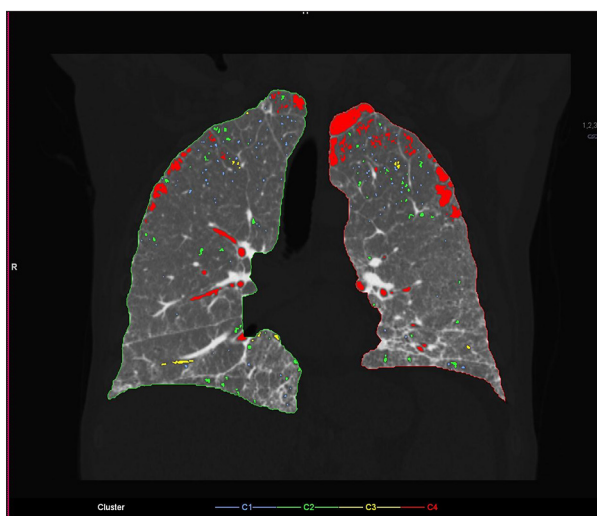
Lung biopsy was not performed because of the presence of emphysema and signs of pulmonary hypertension on echocardiography.

Alpha-1 antitrypsin ( $A_1AT$ ) concentration in serum was within normal limits. Sanger sequencing of four exons (II, III, IV, V) of the *SERPINA1* gene didn't reveal any abnormalities.

Lung emphysema and ILD in the course of chronic visceral ASMD has been diagnosed. Despite marked desaturation on exertion, the resting oxygen saturation was within normal limits. Therefore, the patient has been advised to contact our pulmonary unit in 6 months' time for repeated evaluation and eventual qualification for long-term oxygen therapy (LTOT). Repeated clinical evaluation after 6 months revealed stable pulmonary disease, with no indications for LTOT.

## Discussion

The presented case report concerned a 65-year-old Caucasian male with ASMD recognized in adulthood. The presented symptoms (hepatosplenomegaly, more common childhood infections that later resolved) did not affect the patient's functioning. Because of this, the patient was not motivated to carry out the tests, which have been possible in Poland since around 1980, when the patient was over 30 years old. The definite



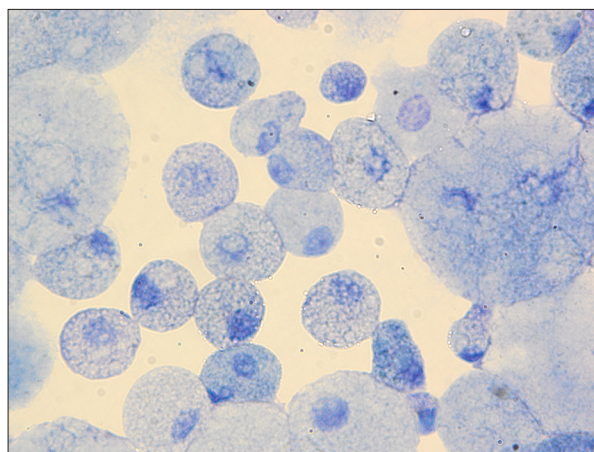
**Figure 3.** Reconstruction (3D Pulmo software) shows emphysema (areas of less than -950 HU) in red.

diagnosis was established at the age of 45 years. From the age of 60 years, the patient noticed increasing dyspnea on exertion. Therefore he was referred to the pulmonary department in search of lung involvement in the course of ASMD. Final diagnosis was emphysema combined with ILD, which seems to be a very rare presentation of chronic visceral ASMD.

The most frequent type of lung involvement in patients with chronic visceral ASMD is ILD with various degrees of fibrosis [7–9]. Lung disease develops as a result of the accumulation of macrophages containing excessive amount of lipids (NP cells) in alveolar septa, lymphatics, bronchial walls, and subpleural spaces [2,3,10]. The confirmation of lung involvement may be obtained by demonstration of lipid-laden macrophages, so-called foamy macrophages, staining blue with MGG (sea blue histiocytes) in lung specimens or in BAL [2]. In the presented patient, we confirmed the presence of foamy macrophages staining with MGG in BAL.

Lung biopsy was not performed because of increased risk of bleeding combined with pulmonary hypertension (PH). Pathogenesis of PH in the course of metabolic disorders is multifactorial, and thus such diseases are listed in the 5<sup>th</sup> PH classification group [11]. In our patient, the principal cause of PH was lung disease presenting with reduced  $T_{LCO}$ .

Among 16 Polish patients with chronic visceral ASMD described by Lipinski et al., ILD has been found in 44% [12]. The detailed characteristics of ILD due to NPD type B was published by Pereira-Freitas et al. in 13 patients [9]. Bilateral interlobular septal thickening and ground-glass opacities have been noted in all of them. Ground-glass opacities were focal in 10 patients and diffuse in 3. In 38%, crazy-paving pattern – defined as interlobular – septal thickening superimposed on



**Figure 4.** Multivacuolated (foamy) macrophages stained blue with May-Grünwald-Giemsa method in bronchoalveolar lavage fluid of patient with Niemann-Pick disease type B. Light microscope, immersion oil, magnification 1000 $\times$ .

ground-glass opacities – was described, the radiological signs suggestive but not pathognomonic for NPD [9]. Pulmonary disease was affecting predominantly lower lobes.

Von Ranke et al. classified the radiological changes seen in HRCT in the course of NPD as a combination of ground-glass opacities, mild smooth thickening of interlobular septa, and interlobular lines, localized mainly in lower lung zones [3]. Nevertheless, two published case reports documented the presence of small lung cysts in the areas of ILD in patients with chronic visceral ASMD [13,14]. In our patient, larger air spaces, described as marginal emphysema, were demonstrated in the upper lobes, in addition to typical ILD in the basal parts. Emphysema coexisting with ILD has not been classified until now as the radiological sign of chronic visceral ASMD.

However, careful review of the literature indicated that such lung appearance of chronic visceral ASMD has been noticed previously. Callahan et al. described in 2018 two siblings with ILD in the course of chronic visceral ASMD [15]. One of them experienced recurrent spontaneous pneumothorax and HRCT revealed upper-lobe-predominant paraseptal emphysema in addition to lower-lobe ILD. Mannem et al. reported a patient with end-stage lung NPD, listed for lung transplantation, in whom upper-lobe-predominant emphysema with superimposed fibrosis in the lower zones was found on HRCT [16]. The presence of centrilobular emphysema was confirmed in lung explants of a patient with chronic visceral ASMD by Ding et al. in the Cleveland Transplantation Center [17]. Therefore, contrary to previous communications, it seems that ILD in the course of chronic visceral ASMD may be composed of emphysema/cysts and ILD.

The findings indicate that lung emphysema/cysts in chronic visceral ASMD may be caused by migration of NP cells into the bronchiolar lumen, leading to air-trapping and airspace enlargement [3]. The other suggested pathomechanism of emphysema is lung injury due to excessive amounts of active sphingolipids [18].

The recognition of emphysema combined with ILD in chronic visceral ASMD requires exclusion of chronic obstructive pulmonary disease (COPD) and  $A_1AT$  deficiency. Our patient has never been a smoker and spirometry revealed no bronchial obstruction. Thus we excluded COPD.  $A_1AT$  concentration was normal, and  $A_1AT$  gene sequencing revealed no pathologic phenotypes; thus emphysema in the course of  $A_1AT$  deficiency was excluded also.

Combined pulmonary fibrosis and emphysema (CPFE), defined as upper-lobe emphysema coexisting with lower-lobe fibrosis, with a usual interstitial pneumonia-like pattern [19], should also be taken into account in differential diagnosis. Absence of honeycombing and finding of ground-glass opacities on HRCT excluded CPFE in the presented patient.

In our patient, plethysmography revealed marked decrease of  $T_{LCO}$ , with normal lung volumes. Combination of emphysema and ILD preserves lung volumes, but  $T_{LCO}$  is usually lowered.

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Such lung function disturbances have been found in CPFE [19] and also in chronic visceral ASMD [20].

It is important to assess pulmonary involvement in chronic visceral ASMD, as it may cause substantial mortality, especially in older patients [21]. Enzyme replacement therapy (ERT) for NPD is not yet commercially available. The patient is a candidate for ERT, as soon as possible in Poland. Patients with progressive ILD and respiratory insufficiency should be offered LTOT and should be listed for lung transplantation. In our patient, repeated clinical evaluation after 6 months revealed stable pulmonary disease; therefore LTOT was not recommended.

## Conclusions

We present a rare type of pulmonary involvement, combined emphysema and ILD, in a nonsmoking, adult patient with chronic visceral ASMD. On such occasions various other causes of emphysema as well as CPFE syndrome should be taken into account in differential diagnosis.

## Conflicts of interest

None.