

## Niemann-Pick Type B long taken for miliary tuberculosis: A Rare cause of interstitial lung disease: A case report

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### Abstract

**Background:** Type B Niemann-Pick disease (NPD) is a rare lysosomal storage disease secondary to a deficiency in sphingomyelinase activity. The accumulation of sphingomyelin occurs in various organs, the lung in particular, the involvement of which determines the prognosis of the disease [1].

**Case presentation:** We report a case of type B NPD disease diagnosed in adolescence who was mistakenly treated as a miliary tuberculosis. The disease was revealed by a dyspnea, with a diffuse interstitial disease and a crazy paving at the chest computed tomography, and many foamy histiocytes with finely vacuolated cytoplasm on the bronchoalveolar lavage.

**Conclusion:** Through this case, we underline the diagnostic difficulty of type B NPD and we recall the elements of orientation towards this pathology.

**Keywords:** Lysosomal storage disorder; Interstitial pulmonary disease; Niemann pick type B; Case report

### 1. Introduction

Niemann-Pick disease (NPD) type B is a rare lysosomal storage disease secondary to a deficiency in sphingomyelinase activity. The accumulation of sphingomyelin occurs in various organs, in particular the lung, which involvement determines the prognosis of the disease [1]. Acid sphingomyelinase deficiency (ASMD) is a rare, autosomal recessive lysosomal disease in the SMPD1 gene. It is historically called Niemann Pick disease. The type b form mainly gives pulmonary involvement and is seen in patients reaching adulthood. It is a disease that remains poorly understood among pulmonologists. Promising new diagnostic and therapeutic recommendations are multiplying. We present a case of an adolescent girl initially treated as miliary tuberculosis without improvement, before referring her to a pulmonologist. We briefly review and discuss aspects of the disease and current challenges, especially in our context.

### 2. Case presentation

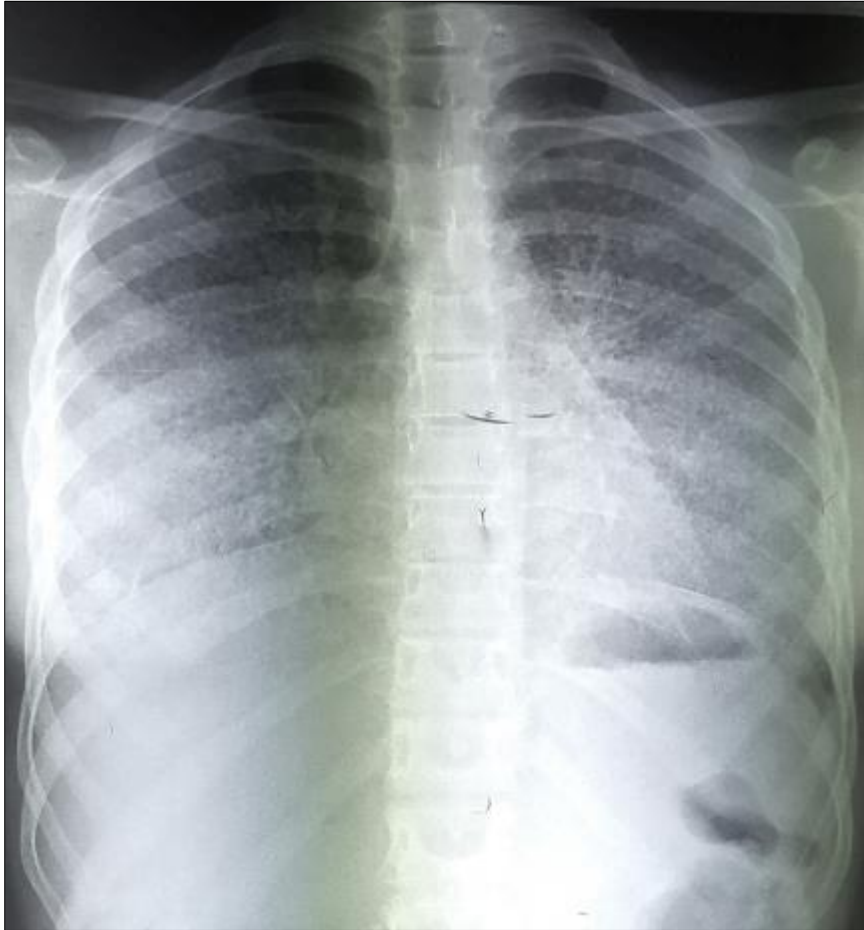
This is a 14 years and 10 months old female patient, born from a consanguineous marriage. She has no history of exposure and was treated for a miliary tuberculosis without bacteriological confirmation due to an interstitial lung

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disease pattern on a chest X-ray, with the notion of a tuberculosis contagion in the family. She received specific tuberculosis treatment, without improvement.

She presented with a minor dyspnea: stage 1 of modified Medical Research Council (m-MRC) scale without other associated signs. She did not have a cough, or hemoptysis, chest pain, dry syndrome, pruritus, or rash. The dyspnea was evolving in a context of apyrexia, without night sweats, without asthenia, anorexia, or weight loss.

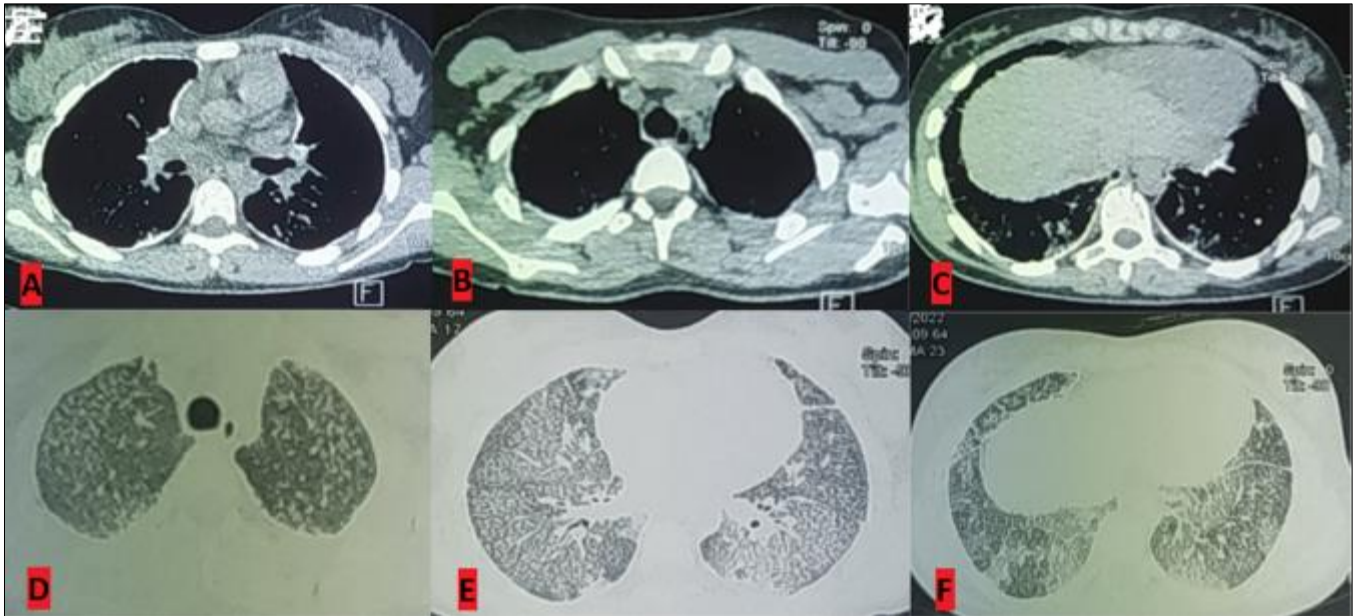
On clinical examination the patient had a Temperature at 36.3 °C, she was eupneic at 22 c/min, her SaO<sub>2</sub> was at 96%, her heart rate was at 88 bpm and her blood pressure was at 100/70mmhg. The pulmonary auscultation found crackles in both lower lobes. The patient did not present any nail clubbing or cardiac failure signs. She weighted 44kg (-1DS) with a 153 cm height (-1DS) making her BMI at 18.79 kg/m<sup>2</sup>. She didn't have hepatomegaly or splenomegaly, and without neurological alterations.



**Figure 1** Chest X-ray showing pulmonary micronodules predominant on the lower halves of the lungs.

The standard Chest X-ray showed pulmonary micronodules predominant at the level of the lower half of the 2 pulmonary hemifields (Figure 1).

She had extensive pulmonary involvement at chest computed tomography (CT) with a diffuse interstitial disease and a radiological pattern of “crazy paving” in the lower and middle lung fields; diffuse intraparenchymal and subpleural micronodules, bilateral basal ground glass with septal and non-septal thickening giving the appearance of crazy paving, with infracentimetric mediastinal lymphadenopathy. The CT scan of the abdomen did not show a hepatomegaly or splenomegaly (Figure 2).



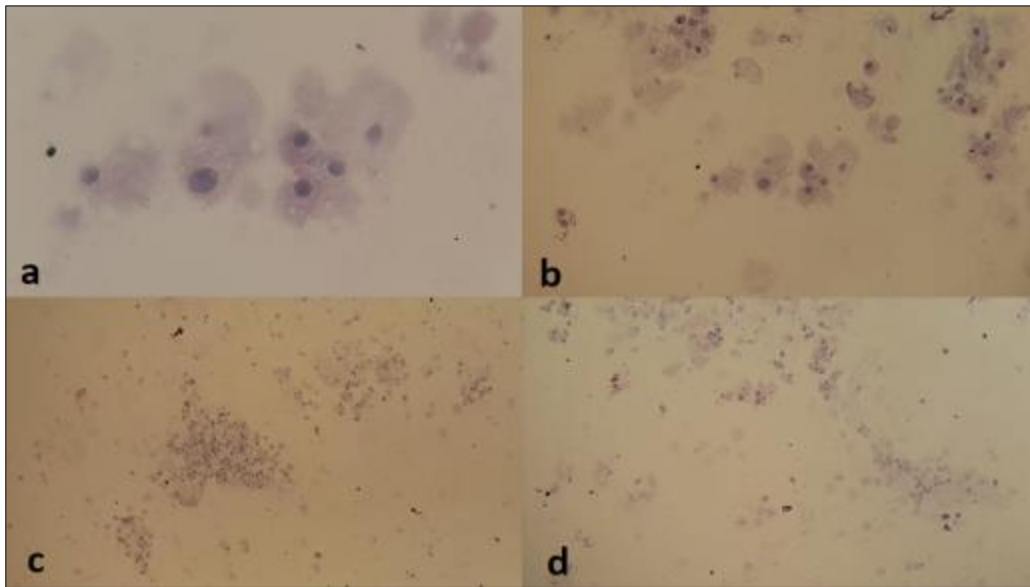
**Figure 2** Chest CT scan in axial section (A+B+C = mediastinal window, D+E+F = parenchymal window), showing the diffuse interstitial disease

The bronchial endoscopy (Figure 3) showed a healthy endoscopic appearance. bronchoalveolar lavage (BAL) fluid was slightly lactescent, analysis of the liquid collected revealed a hypercellularity predominantly made of macrophage (80%) and many foamy histiocytes with finely vacuolated cytoplasm. The pathology of the bronchial biopsy, noted a moderately inflammatory mucosa, coated by respiratory-like epithelium, the BAL cultures were negative for bacteria and mycobacteria (Figure 4).

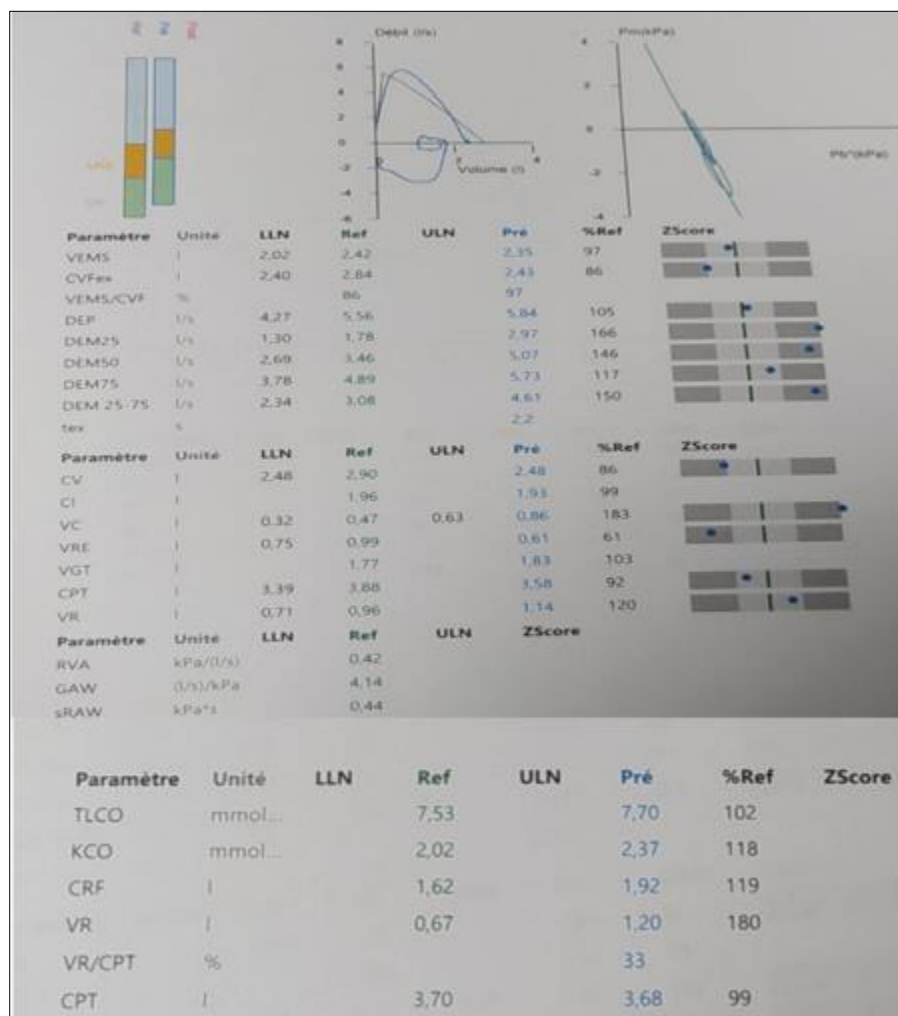


**Figure 3** Endoscopic appearance without particularities (before (A) and after (B) staged biopsies)

Her pulmonary function tests demonstrated preserved lung volumes (FEV1: 2350 ml (97%), FVC: 2430 ml (86%), and FEV1/FVC: 97) and a normal DLCO (diffusion capacity for carbon monoxide): 102%. Her blood gas at room air were normal, and she covered 70% of theory distance without desaturation in the 6-minutes walking test (Figure 5). The echocardiography did not show any sign of cardiac dysfunction or pulmonary hypertension. Liver function was normal, but blood tests found hyperlipidemia with high levels of triglycerides and low level of high-density lipoprotein (HDL). Renal function was normal.



**Figure 4** Histopathological features with the papanicolaou stain (x40)



**Figure 5** The plethysmography and DLCO.

Immunological blood analyses including anticytoplasmic antibodies, antiglomerular basal, antinuclear antibodies, rheumatoid factor and antibodies to citrullinated peptide were negative. The brain magnetic resonance imaging revealed no abnormalities.

Faced with this picture of diffuse infiltrating lung disease with the presence of foamy histiocytes, and altered lipid balance, a lipid storage disease was strongly suspected; we completed the study of leukocyte activity of sphingomyelinase to retain the diagnosis of NPD type B.

Since the evaluation of the pulmonary function was good, it was decided to maintain active surveillance and periodic reassessment of lung function.

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### 3. Discussion

Niemann-Pick disease type NPD A patients have mainly neurological impairment and a poor prognosis with a median lifespan of 3 years after birth [1]. In contrast, NPD B patients reach adulthood, The Niemann-Pick disease type C, initially grouped with ASMD (Acid sphingomyelinase deficiency (ASMD)), is driven by other pathogenesis, different genetic disorders and central nervous system is mainly involved [1]. The exact prevalence of lung involvement in NP disease is difficult to determine; however, it remains relatively rare in adults [2]. Niemann-Pick type B disease exhibits great variability in clinical manifestations and the severity of symptoms [1]. The symptomatology is very variable and non-specific [3].

Indeed, bronchopulmonary involvement may be proportional to the degree of protein activity deficit [4]. As for our patient, this mutation is common in patients from North Africa [5].

On imagery, the disease is manifested by non-specific opacities, observed in 90 to 98% of cases; a non-specific interstitial syndrome on the chest X-ray with basal predominance, The CT scan shows a crazy paving pattern with the association of thickening of the interlobular septa, intralobular reticulations and ground glass [6]. These lesions predominate at the level of the bases [6].

For our patient, according to the radiological aspect, the notion of tuberculosis contagion and the epidemic context, a miliary tuberculosis was initially made, with antibacillary treatment but without improvement, the absence of other clinical manifestations also had an impact on the diagnostic difficulty, mainly the absence of a hepato-splenomegaly.

Thrombocytopenia and mixed dyslipidemia are typical biological features reported in NPD B patients [7].

As recommended; the diagnosis of the disease is confirmed by the dosage of the activity of the enzyme, genetic detection of pathogenic SMPD1 variants may be used for diagnostic for second intention [7], the accessibility to those tests in our context remains difficult. The study of sphingomyelinase activity can be done on leukocytes and skin fibroblasts [6].

Pulmonary function tests help to assess the consequences and assess the accumulation of sphingomyelin, there is a weak correlation between the extent of the radiological abnormalities and the modifications of the pulmonary function tests [8], which can join the discrepancy between the radiological damage and the normal function in our case. The decrease in pulmonary compliance and DLCO remains more characteristic, longitudinal studies demonstrated slow but progressive deterioration in lung function tests [8].

The management of this disease is currently based on symptomatic measures and supportive care. Whole lung washing, has shown efficacy in few cases reports but remains a high-risk procedure with only temporary benefit [7,9].

Splenectomy must be avoided as it may worsen hyperlipidemia profile, the vaccination is warranted [7,9].

The discussion of the effect of steroids remains an open question [9].

Lung transplantation may be considered as a treatment option for patients with severe lung involvement and no extrapulmonary organ dysfunction, unless considered for multi-organ transplantation [7,9].

New enzyme replacement therapies are rising with the potential to modify the natural history of the disease [7,9,10,11]

Olipudase alfa, a recombinant human acid sphingomyelinase, is an enzyme replacement therapy for the treatment of non-neurological manifestations of acid sphingomyelinase deficiency that has shown promising results[12], a multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of Olipudase alfa with significant results in reduction in spleen and liver volume and improvement in lung function[12].

Olipudase alfa is not currently available but compassionate use is possible as is the case in several countries. Since respiratory involvement is a leading cause of death in NPD type B disease [7,12], early treatment with enzyme therapy can prevent mortality and improve quality of life. Access to these therapies remains more difficult in our context.

#### *List of abbreviation*

- NPD: Niemann-Pick Disease
- AMSD: Acid sphingomyelinase deficiency
- FEV1: Volume exhaled at the end of the first second of forced expiration
- FVC : Forced vital capacity
- FEV1/FVC: Tiffeneau-Pinelli index
- DLCO: diffusion capacity for carbon monoxide

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#### **4. Conclusion**

Niemann-Pick disease is a rare systemic overload disease that can affect the lung. Early diagnosis is still lacking, mainly due to the lack of knowledge of this disease. There are no specific symptoms, the association of hepatosplenomegaly with interstitial lung disease should suggest an overload disease.

As presented in our case; rare congenital diseases can present at a more advanced age, hence the importance of awareness and information for early diagnosis for a better prognosis.

Niemann-Pick type B disease keeps symptomatic treatment and supportive care, enzyme therapy can bring new hope and improve prognosis, quality of life and extend life expectancy.

A multidisciplinary team should be mobilized, especially to improve access to diagnostic means and better care for these patients.

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#### **Compliance with ethical standards**

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##### *Disclosure of conflict of interest*

The authors declare no conflict of interest regarding the publication of this article.

##### *Statement of informed consent*

Informed consent was obtained from the patient included in the study. The patient information was kept confidential during and after study period.

##### *Authors' contribution*

Mohamed Ijim, Imane Saidi, Salma Ait Batahar, Lamyae Amro, conceived the idea, provided the framework and edited the manuscript. MI performed the extensive literature search and wrote the initial drafts and provided the clinical data and searched the literature. Latifa Elouazani, Fatima Ezzahra Hazmiri provided the pathology study. All the authors contributed to the clinical care of this case, and they all approved the final manuscript.

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