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(CASE REPORT)

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Adult niemann-pick disease: A case report

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Abstract

Niemann-Pick disease (NP) is a rare lysosomal storage disorder, inherited in an autosomal recessive manner. It is a sphingomyelin-cholesterol lipidosis associated with the accumulation of foam cells. It is divided into two entirely distinct entities on metabolic, biochemical, and genetic levels: NP A/B and NP C.

Diagnosis is established by clinical and biological presentation, notably through bone marrow examination (myelogram), and low enzymatic activity of acid sphingomyelinase for types A and B. Whereas for type C, the filipin test on cultured skin fibroblasts is no longer considered the gold standard; new diagnostic approaches are currently being investigated.

Genetics remains highly preferred for diagnosis. Normal enzymatic levels do not exclude the diagnosis in the presence of a highly suggestive clinical phenotype. The aim of our study is to present the clinical, biological, histological, and radiological aspects of Niemann-Pick disease, in the context of a clinical case of a male patient hospitalized in the Hematology Department at Avicenne Military Hospital in Marrakech.

We report the case of a 57-year-old patient, born of consanguineous marriage, with a personal history of appendectomy and a family history of a brother treated for and deceased from tuberculosis. The patient was admitted for progressive abdominal pain and left hypochondrial heaviness. Clinical examination revealed splenomegaly and osteoarticular pain on palpation, associated with nocturnal sweats evolving in the context of a general deterioration of health. The myelogram revealed numerous very large foam cells with cytoplasm filled with blue granulations stained by May Grunwald Giemsa (MGG), giving a characteristic "sea blue" appearance typical of Niemann-Pick disease. Biochemistry showed disrupted lipid profiles with collapsed HDL cholesterol in the absence of enzymatic alteration of acid sphingomyelinase. Histology revealed macrophage overload with foam-like cytoplasm appearing sea blue. Imaging confirmed nodular splenomegaly.

With this data, the diagnosis of Niemann-Pick disease type B was made, despite the absence of enzymatic imbalance, which is only specific in cases of deficiency. This highlights the complexity of the diagnosis.

Our study demonstrates that the myelogram is a crucial examination for the detection of Niemann-Pick disease. The normal enzymatic assay despite a typical phenotype of Niemann-Pick type B highlights the complexity of the diagnosis and the lack of specialized laboratories for these assays.

Keywords: Inherited Diseases; Myelogram; Acid Sphigomyelinase; Macrophages; Splenomegaly

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1. Introduction

Niemann-Pick disease (NP) is a rare entity among autosomal recessive inherited diseases, with a prevalence at birth estimated at 1/100,000. It can be considered the most characteristic among sphingolipidoses and can occur in any population [1].

Niemann-Pick diseases are a group of storage diseases, divided into three groups: NPA, NPB, and NPC. NP type A (the rapidly progressive neuropathic form) and type B (the non-neuropathic form with variable age of onset) are caused by a deficiency of the lysosomal enzyme acid sphingomyelinase (ASM). Whereas type C may occur due to defects in a transmembrane protein Niemann-Pick C1 (NPC1) or soluble Niemann-Pick C2 (NPC2) [2-3]. At the cellular level, these mutations result in characteristic lipid transport abnormalities, leading to a number of cellular responses [4-5].

The diagnosis is established by clinical and biological presentation, notably bone marrow examination (myelogram), and low enzymatic activity of ASM for types A and B. However, for type C, the filipin test on cultured skin fibroblasts is no longer considered the gold standard. New diagnostic approaches are currently being tested [6]. Genetic testing remains highly preferred for diagnosis [7].

In our study conducted at the Hematology Department of Avicenne Military Hospital in Marrakech, we present the case of a 57-year-old adult patient with a clinical history characterized by a two-year onset of symptoms including splenomegaly, osteoarticular pain, and hematological disorders.

2. Case report

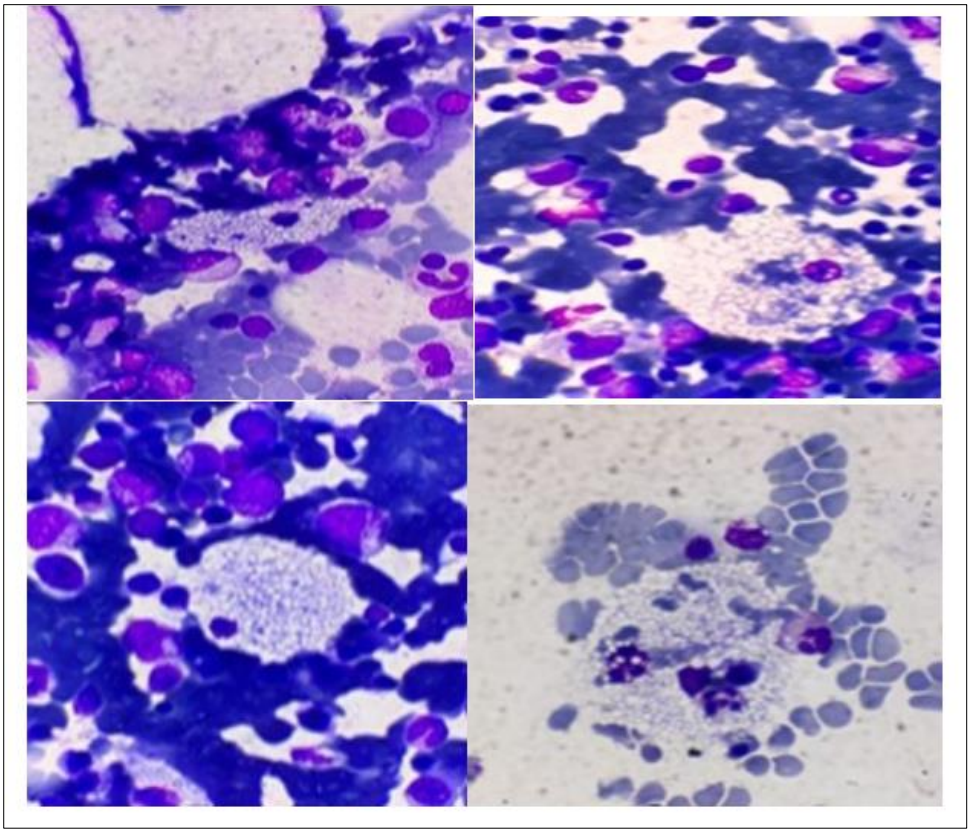

Figure 1 "Sea-blue" image on myelogram performed at the Hematology Laboratory, HMA

The patient, a 57-year-old individual from a consanguineous marriage, had a personal history of appendectomy and a family history of a brother treated for and deceased from tuberculosis. He was admitted due to progressive left hypochondrium pain and abdominal discomfort. Clinical examination revealed splenomegaly and osteoarticular pain upon palpation, along with nocturnal sweats in the context of overall general deterioration.

Laboratory tests showed thrombocytopenia, while the myelogram revealed numerous large foamy cells with cytoplasm filled with blue-stained granules upon May Grunwald Giemsa (MGG) staining, characteristic of Niemann-Pick disease (Figures 1). An atherogenic lipid profile with decreased HDL and hypertriglyceridemia, as well as hyperbilirubinemia, was also observed.

Histology demonstrated macrophage overload with foamy cytoplasm displaying a characteristic "sea-blue" appearance, suggestive of a lipid storage disorder, although not specified. Imaging confirmed nodular splenomegaly.

Subsequently, enzymatic assays for acid sphingomyelinase and β-glucocerebrosidase were conducted and found to be normal.

3. Discussion

Niemann-Pick disease is a rare lysosomal storage disorder, inherited in an autosomal recessive manner. It is a sphingomyelin-cholesterol lipidosis associated with the accumulation of foamy cells [8]. Currently, three forms are described:

- Types A and B: a pathology resulting from deficiency of acid sphingomyelinase due to SMPD1A mutation [9].
- Type C: a defect in intracellular cholesterol trafficking due to NPC1 or NPC2 mutations [10,11].

These three forms differ from each other in terms of age of onset, neurological manifestations, and accumulated substrate. Niemann-Pick diseases types A and B have an incidence of 1 in 250,000 individuals, while type C's prevalence is difficult to ascertain (likely underdiagnosed), estimated to be around 1/130,000 [12,13]. The clinical presentation of Niemann-Pick disease is heterogeneous and varies according to the type. Onset age is typically in childhood. Until now, the adult form has only been described in types B and C [5,14,15,16].

Niemann-Pick disease type A is a very severe subtype characterized by neurological involvement, appearing at a very young age. Neurodegeneration progresses rapidly and leads to death within three years [17,14].

On the other hand, type B is generally later onset and less severe, with onset ranging from childhood to adulthood, and a good prognosis for survival in the absence of neurological involvement. Only 6% of the disease affects the adult population [17,18,19,20,21,13].

Although the diagnosis is typically established in childhood, the disease can rarely be first recognized during adolescence or adulthood. As demonstrated by Lipinski in a study of 16 patients with Niemann-Pick type B, 12 cases were diagnosed in childhood and 4 in adulthood. This is comparable to the retrospective series by O. Lidove involving 28 cases, which showed that the diagnosis is often made before the age of thirty, with a mean age of 11 years [21,22].

Family consanguinity is common, confirming its genetic nature [16]. Willvonseder et al. reported a case of NP in a patient who had three affected brothers [23]. However, there are cases described in the literature of Niemann-Pick types A, B, and C that do not exhibit consanguinity [24,25,26,14]. The case presented in this study is a 57-year-old male patient from a consanguineous marriage.

Our patient had a history of appendectomy one year prior. In Thurberg's study, sphingomyelin accumulation was multi-organ and present in cells from various organs [27]. More recent studies illustrate that all types of cells in the body are susceptible to accumulating pathological substrates, including sphingomyelin [28,29]. This leads us to speculate that his appendicitis may be related to this disease.

In the literature, a tuberculous-like miliary pattern is found in Niemann-Pick type B [26]. Our patient had a brother who was treated for and deceased from tuberculosis. This raises the hypothesis: was it indeed tuberculosis or a misdiagnosis that obscured Niemann-Pick disease type B?

These mentioned hypotheses could be associated with the overall clinical picture to guide the diagnosis towards Niemann-Pick disease type B. Patients with Niemann-Pick disease exhibit signs of multi-organ involvement, including hepatomegaly, splenomegaly, and/or hepatosplenomegaly. This has been observed in the series by Schuchman and McGovern et al., where hepatosplenomegaly was reported as the most constant and predominant sign, with a higher prevalence of splenomegaly than hepatomegaly [17,30].

At the age of 57, our patient presented with symptomatic splenomegaly from the outset. Two main explanations can be considered for this situation. Either the patient had previously experienced undiagnosed asymptomatic splenomegaly, or the splenomegaly was consistently present but neglected by the patient. This aligns with a case of Niemann-Pick type B in the sixth decade of life described by Simoes and Maia, where splenomegaly was the first manifestation of the disease. It is also comparable to some cases of Niemann-Pick type C described by Dvorakova et al. at the age of 53 [31].

Our patient reported experiencing joint pains, which is consistent with cases reported in the literature for Niemann-Pick type B. In the prospective study by McGovern et al. involving 59 patients with Niemann-Pick type B, joint or limb pains accounted for 39% of physical signs [24].

However, osteoarticular involvement has not been reported in any cases of Niemann-Pick type C [32,33].

The myelogram described by Candoni revealed marine blue histiocytosis associated with a mild phenotype of Niemann-Pick type B in a 44-year-old man presenting with splenomegaly and mild thrombocytopenia. The diagnosis was guided by morphological findings in bone marrow smears of foamy and marine blue histiocytes [34].

The diagnosis of this rare disease remains quite complex, as it presents with a wide variety of symptoms. In our 57-year-old patient, the combination of thrombocytopenia, splenomegaly, and the presence of sea-blue histiocytes on myelogram was suggestive of Niemann-Pick disease type B. Therefore, an assay for acid sphingomyelinase was requested and found to be normal.

Lipid abnormalities are characteristic of Niemann-Pick diseases A and B, showing increased levels of total cholesterol, LDL, and triglycerides, as well as decreased levels of HDL cholesterol.

This dyslipidemia profile was observed in our patient. His lipid profile showed a low level of HDL (<0.05) along with elevated levels of triglycerides and LDL. These findings are consistent with those reported by other authors. In the study by McGovern et al., 59 patients with Niemann-Pick disease type B were included. Most patients exhibited an atherogenic lipid profile, with the most characteristic lipid abnormality being a low HDL level (74% of patients) compared to individuals of the same age and sex [24].

Histological examination plays a crucial role in exploring pathological processes and aiding in diagnosis. Our patient underwent splenic biopsy, revealing parenchymal inflammation rich in macrophages with foamy cytoplasm, a characteristic feature of Niemann-Pick disease. This aligns with the findings of Escobar et al., who reported a case of Niemann-Pick type B disease where splenomegaly was associated with hematological disorders. The splenic biopsy showed extensive expansion of the red pulp by numerous macrophages with large, foamy cytoplasm [35].

4. Conclusion

Niemann-Pick disease is a rare autosomal recessive disorder. It is a lysosomal storage disease that divides into two distinct entities on a genetic and metabolic level: Types A and B, and Type C.

Niemann-Pick type B disease is the visceral form of acid sphingomyelinase deficiency (ASM) with an incidence remaining at 1/200,000. The clinical presentation of Niemann-Pick disease is extremely heterogeneous due to its largely unexplained pathophysiology. Symptoms, rate of progression, and life expectancy vary greatly.

The diagnosis of Niemann-Pick type B disease relies on clinical evaluation, laboratory testing, including measurement of acid sphingomyelinase activity, and/or genetic studies, which remain the most reliable tests. A normal enzymatic assay does not rule out the diagnosis in the presence of a highly suggestive clinical phenotype. Our study demonstrates the importance of myelogram testing in the detection of Niemann-Pick disease. The normal enzymatic assay despite a typical phenotype of Niemann-Pick type B disease highlights the complexity of diagnosing this condition.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All the data has been collected anonymously following patient confidentiality

Statement of informed consent

Informed consent was obtained from all individual participants included in the study. .

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