Case Study

Delayed Diagnosis of Niemann-Pick Disease in a 31-year-old Caucasian Woman

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Abstract: Niemann-Pick disease (NPD) is a rare inherited autosomal recessive neurodegenerative disease usually diagnosed at young age. Type A and B Patients are characterized by *Sphingomyelin phosphodiesterase 1* (*SMPD1*) gene mutation and frequently have ataxia, dystonia, early-onset cognition decline or even dementia. However, type C patients have *NPD Type C* (*NPC1*) gene mutation and can show a wide spectrum of clinical presentations, leading to potential delayed diagnosis. A 31-year-old Caucasian woman presented with dyspnea on exertion, massive splenomegaly and progressive thrombocytopenia. CT showed multiple bilateral lung nodules. Lung biopsy demonstrated intra-alveolar collection of foamy, vacuolated histiocytes. Bone marrow biopsy revealed collection of foamy, vacuolated histiocytes characteristic of NPD. Molecular test detected heterozygous A196P mutation of *SMPD1* gene and one heterozygous mutation of *NPC1* gene. The diagnosis of NPD type C is rendered by biochemical testing that demonstrates impaired cholesterol esterification and positive filipin staining in cultured fibroblasts.

Keywords: Niemann-Pick disease, bone marrow, lung, diagnosis, gene mutation

Introduction

Niemann-Pick disease (NPD) is a heterogeneous group of lysosomal lipid storage disorders. There are four most commonly recognized forms of the disease: Types A, B, C, and D. Types A and B result from mutations in the *Sphingomyelin phosphodiesterase 1* (*SMPD1*) gene coding for the Sphingomyelin phosphodiesterase 1, also known as lysosomal enzyme acid sphingomyelinase (ASM). Patients with Type A, an acute infantile form, show severe hepatosplenomegaly, rapid progressive neurodegenerative disorders and failure to thrive during the first year of life. They seldom survive beyond the third year of life. Patient with Type B are usually diagnosed in early life with profound hepatosplenomegaly, liver failure, elevated serum triglyceride and pulmonary malfunction, though the patients could survive into adulthood [1]. 95% of patients with NPD Type C (NPC) have mutations in the *NPC1* gene, which encodes a lysosomal /endosomal transmembrane protein. Only very rare cases have mutations in the *HE1/NPC2* gene, which encodes a soluble lysosomal protein with cholesterol-binding properties. Niemann-Pick Type C disease has a wide spectrum of clinical presentations, including hepatic and pulmonary disease, and a range of neuropsychiatric disorders. Type D Niemann-Pick involves a defect that interferes with the movement of choles-

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terol between brain cells. It is now thought to be a variant of type C. NPD is an autosomal recessive disease [2]. Here we report a case diagnosed in a 31-year-old Caucasian female with lung involvement and later proved to be heterozygous mutation both in *SMPD1* and in *NPC1* genes.

Case Report

A 31-year-old female patient initially presented with intermittent fatigue, low grade fever and dyspnea on exertion without neurologic symptoms. Chest computed tomography showed multiple bilateral lung nodules [Figure 1A]. Pulmonary functional tests (PFT) suggested a restrictive lung disease. She developed massive splenomegaly and progressive thrombocytopenia over one year period. Sarcoidosis was considered, and patient was empirically treated with steroids with transiently improved PFTs. Bone marrow examination demonstrated collection of foamy, vacuolated histiocytes characteristic of NPD [Figure 1B]. Endoscopic transbronchial biopsy showed lung tissue with intra-alveolar collection of foamy, vacuolated histiocytes consistent with involvement by NPD [Figure 1C]. Molecular test detected heterozygous A196P mutation of *SMPD1* gene in isolated leukocytes. Leukocyte acid sphingomyelinase activity was 21, with the normal range between 30 and 120. It is slightly lower but well above those levels associated with classic Niemann Pick Disease. Skin fibroblast sphingomyelinase level was greater than 10% of control, which was relatively normal. One heterozygous mutation of *NPC1* gene was detected: c.3570_3573dupACTT; p.A1192fs, with a duplication of ACTT from 3570 to 3573 at exon 23 resulting in frame shift. *Niemann Pick C-2* (*NPC2*) sequence analysis showed no mutations. The esterification of cholesterol of cultured skin fibroblast in response to stimulation of LDL cholesterol uptake was significantly depressed relative to normal and similar to NPC positive control. Filipin staining of free cholesterol was also abnormal as seen in NPC. The activity level of chitotriosidase was 287.3 nmol/hr/ml, with the normal value of being less than 78.5 nmol/hr/ml.

Discussion

There are four types of NPD: Type A, B, C and D. Both Type A and Type B patients demonstrate insufficient acid sphingomyelinase (ASM) activity. Type A and Type B are more common. It is estimated that the incident rate for type A and type B combined is 1: 250,000 [3]. In contrast to NPD type A, type B disease shows variable phenotypic features with less severe clinical presentation due to residual enzymatic activities. Both types demonstrate deficiency of acid sphingomyelinase resulted from hereditary mutation of its gene *SMPD1*. While A196P mutation of *SMPD1* has been previously described in type B NPD with mild phenotypic presentation, the recessive trait of the disease needs *SMPD1* mutation in both alleles for patient to exhibit clinical symptoms. The *SMPD1* gene resides within an imprinted region on chromosome 11, and is preferentially expressed from the maternal chromosome [4]. It is highly likely that heterozygous patient can be symptomatic due to inheritance of a single, severe *SMPD1* mutation on the preferentially expressed maternal chromosome.

NPD type C is an autosomal recessive diseased caused by mutations of *NPC1* or *NPC2* gene [5]. The prevalence rate of type C is estimated to be 1: 100,000 in Europe [6]. Approximately 95% of patients have mutations in the *NPC1* gene, which is located at chromosome 18q11-q12. It encodes a large membrane glycoprotein in endosomes. *NPC2* gene encodes a small soluble lysosomal protein that binds cholesterol with high affinity. *NPC2* is involved in rare families (about 30 are known to date). Mutations in the *NPC1* or *NPC2* genes result in impairment in processing and utilization of endocytosed cholesterol that is critical in cholesterol storage and secondary alterations of sphingomyelin metabolism in extra neural tissues [6, 7]. Mutations at both alleles are usually required for manifestation of the disease. The clinical presentation of NPC is extremely

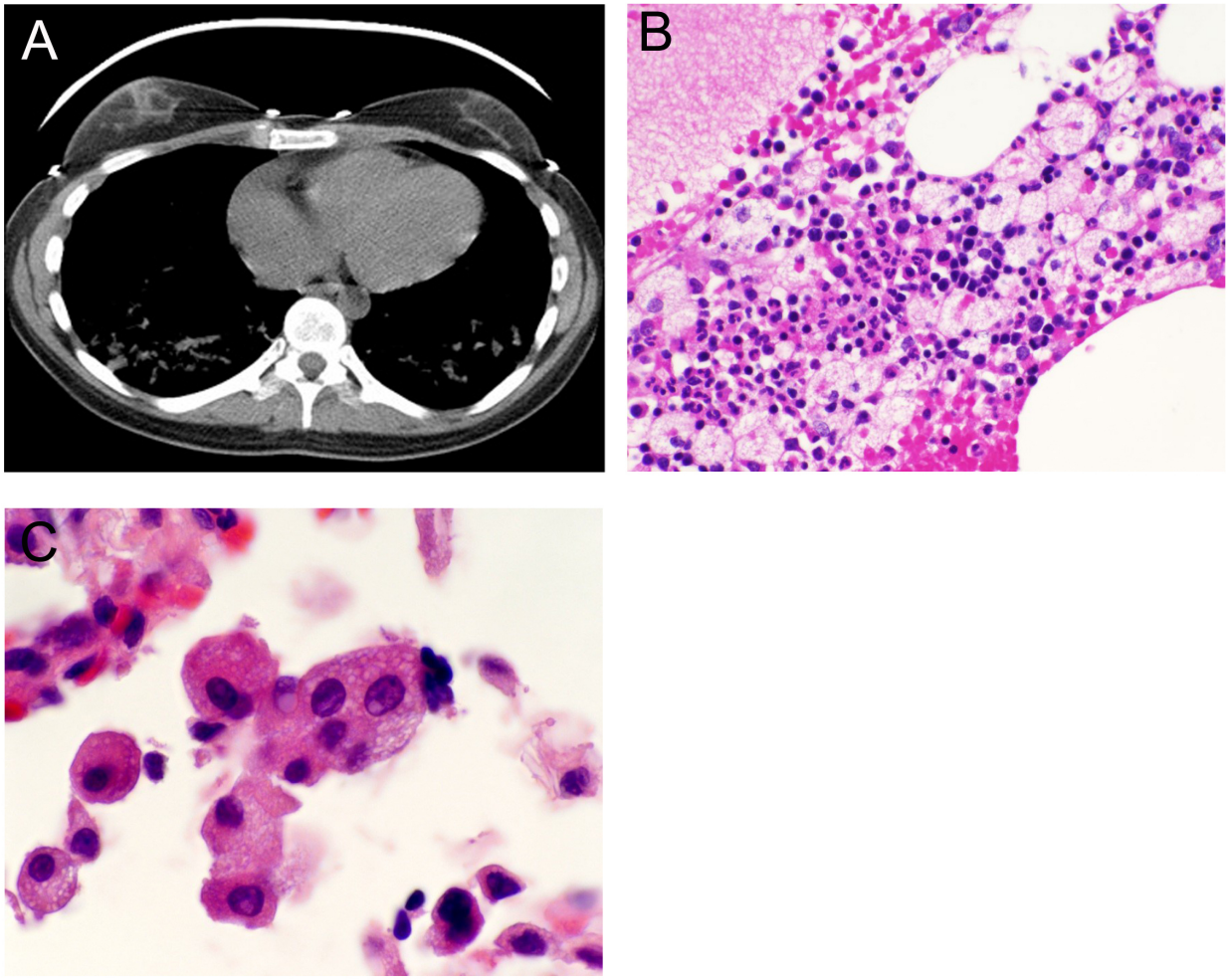

Figure 1: A. Chest computed tomography showed multiple bilateral lung nodules. B. Bone marrow examination demonstrated collection of foamy, vacuolated histiocytes characteristic of NPD. C. Endoscopic transbronchial biopsy showed lung tissue with intra-alveolar collection of foamy, vacuolated histiocytes consistent with involvement by NPD..

heterogeneous, with an age of onset ranging from newborn until late adulthood. The lifespan of the patients varies between a few days until over 60 years of age, although a majority of cases die between 10 and 25 years of age.

It is very unusual for the patient to be heterozygous for both NPD Types B and C mutations and the patient was symptomatic. The question is: are the symptoms of the patient caused by the *SMPD1* gene or *NPC1* gene or the interaction between these two genes? Among all the variants of Niemann-Pick disease, Type B is the one that is most frequently associated with lung involvement [8]. The deleterious mutation, A196P, is located at the exon 2 of the *SMPD1* gene. It is a common mutation in Scottish/English patients and is associated with an adult form of NPD type B [9]. The diagnosis of ASM deficiency is established when residual ASM enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts is less than 10% of controls. In our patient, her leukocytes ASM activity was slightly lower than normal value but much higher than the

expected one for NPD. Her cultured skin fibroblasts ASM activity was within normal range. Therefore, the diagnosis of NPD Type B is not favored.

The diagnosis of NPC is confirmed by biochemical testing that demonstrates impaired cholesterol esterification and positive filipin staining in cultured fibroblasts. Our patient shows positivity of both these tests. Most NPC patients have two *NPC1* mutations. However, a small portion of patients show only one mutation or no detectable mutations. There is great variability in mutations within the *NPC1* gene because the gene is relatively large and most mutations are private to their own family. There might be correlation between genotype and phenotype. Because of the rarity of the disease, it is hard to link every specific mutation to its phenotype [10]. The mutation in our patient is not a common one. Most likely it is private to her own family. It seems that her presentation was relatively milder. However, it is not clear why she was symptomatic despite of her heterozygous status. Was there maternal/paternal imprinting? Did the heterozygous *SMPD1* gene interact with the heterozygous *NPC1* gene and enhance the expression of *NPC1* gene? Further studies are needed to elucidate the pathogenesis in this case.

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