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LETTER TO THE EDITOR

Hepatosplenomegaly, pneumopathy, bone changes and fronto-temporal dementia: Niemann–Pick type B and SQSTM1-associated Paget's disease in the same individual

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Abstract

Data from exome sequencing show that a proportion of individuals in whom a genetic disorder is suspected turn out to have not one, but two to four distinct ones. This may require an evolution in our diagnostic attitude towards individuals with complex disorders. We report a patient with splenomegaly, pneumopathy, bone changes and fronto-temporal dementia (FTD). "Sea-blue histiocytes" in his bone marrow pointed to a lysosomal storage disease. Homozygosity for a pathogenic mutation in the *SMPD1* gene confirmed Niemann–Pick disease type B (NPD-B). Mild cognitive impairment and abnormal brain FDG PET were consistent with FTD. We initially tried to fit the skeletal and neurologic phenotype into the NPD-B diagnosis. However, additional studies revealed a pathogenic mutation in the *SQSTM1* gene. Thus, our patient had two distinct diseases; NPD-B, and Paget's disease of bone with FTD. The subsequent finding of a mutation in *SQSTM1* gene ended our struggle to explain the combination of findings by a singular "unifying" diagnosis and allowed us to make specific therapeutic decisions. *SQSTM1* mutations have been reported in association with FTD, possibly because of defective autophagy. Bisphosphonates may be beneficial for PDB, but since they are known to inhibit acid sphingomyelinase activity, we refrained from using them in this patient. While the principle of looking for unifying diagnosis remains valid, physicians should consider the possibility of co-existing multiple diagnoses when clinical features are difficult to explain by a single one. Accurate diagnostic work-up can guide genetic counseling but also lead to better medical management.

Keywords Niemann–Pick type B · Paget's disease of bone · Lysosomal storage disease · Acid sphingomyelinase · Interstitial pulmonary disease

Abbreviations

ALP	Alkaline phosphatase
ASM	Acid sphingomyelinase
DLCO	Transfer capacity of the lung for carbon monoxide
ERT	Enzyme replacement therapy
FTD	Fronto-temporal dementia
HRCT	High-resolution computed tomography
LSD	Lysosomal storage disease
NGS	Next-generation sequencing
NPD-B	Niemann–Pick disease type B
NV	Normal value
OMIM	Online Mendelian inheritance in man
PDB	Paget's disease of bone
SMPD1	Sphingomyelin phosphodiesterase 1
S1P	Sphingosine-1-phosphate
SQSTM1	Sequestosome 1

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TBS Trabecular bone score
99Tc Technetium 99 isotope

Introduction

Niemann–Pick disease type B (NPD-B, OMIM: 607616) is an autosomal recessive hereditary lysosomal storage disease (LSD) due to acid sphingomyelinase (ASM) deficiency which causes accumulation of sphingomyelin. The clinical spectrum varies widely, with an age of onset ranging from early childhood to adulthood. NPD-B is characterized by hepatosplenomegaly with thrombopenia and progressive deterioration of pulmonary function due to accumulation of vacuolated lipid-filled macrophages, known as Niemann–Pick cells [1]. The majority of reports concern infantile forms; the adult-onset presentation is less described and still poorly characterized. Treatment of NPD-B is mainly supportive. Bone marrow transplantation has been undertaken, but the associated morbidity and mortality limits its use [2]. A multicenter, randomized phase 2/3 study with recombinant human acid sphingomyelinase (Olipudase®, Genzyme) is currently ongoing to evaluate efficacy and safety [3].

Only few reports mention skeletal involvement in NPD-B and all of them focus on osteoporotic changes and fracture risk [4]. We describe an individual with mutation-proven NPD-B, bone changes and fronto-temporal dementia (FTD; OMIM: 616437), whom we found to have polyostotic Paget's disease of bone (PDB, OMIM: 167250) associated with an heterozygous missense mutation in the *SQSTM1* gene. While the majority of PDB cases are sporadic, familial cases are well known; interestingly, SQSTM1 mutations occur both in familial and in sporadic cases [5]. We discuss the situation of multiple genetic diagnosis in a single patient, which seems to be more frequent than hitherto perceived, and challenges our conservative diagnostic thinking.

Materials and methods

Patient description

A 51-year-old man of Portuguese origin was referred to the Respiratory Medicine Division to investigate exertional dyspnea of recent onset. His neonatal and pediatric history was unremarkable; at age 12 years splenomegaly was observed, but its etiology remained unclear. At age 25 years, elevated liver enzymes were found with normal liver function. At age 45 years, he developed liver steatosis and portal hypertension. Family history was negative for similar observations and there was no known consanguinity.

Results

Physical examination revealed a 170 cm tall, 71 kg weight man, with normal blood pressure and 92% blood oxygen saturation, bibasilar crackles on lung auscultation, digital clubbing, and an enlarged spleen. There was no jaundice. Neurological examination was normal. He had no musculoskeletal complaints. Laboratory evaluation showed thrombocytopenia 58,000 cells/mm^3 (NV 150,000–350,000) and leucopenia 3900 cells/mm^3 (NV 4000–10,000). Aminotransferases in plasma, as well as calcium and phosphorus levels in blood and urine were in the normal range. 25OH-vitamin D was 19 ng/ml (optimal status > 30). Lung function tests showed a mild restrictive pattern with total lung capacity at 76% of predicted, and a mild alteration of the carbon monoxide transfer factor (DLCO) at 47% of predicted. Arterial blood gases analysis showed hypoxemia (partial oxygen pressure 62 mmHg), and no hypercapnia. Chest radiograph and high-resolution computed tomography (HRCT) scan demonstrated a multifocal interstitial "crazy paving" pattern of the lung parenchyma. Abdominal magnetic resonance revealed increased liver and spleen size (25 cm at longest axis for the latter) along with multiple splenic nodules (Fig. 1). Heterogeneous lytic and sclerotic lesions with corticomedullary dedifferentiation, coarse trabeculation and cortical thickening were noted in the HRCT scan at the right iliac bone, right proximal femur, posterior skull and left distal humerus. Tc99-bone scintigraphy showed increased uptake in those sites (Fig. 2). Assessment of lumbar spine (L1–L4) by DXA showed a BMD of 0.854 g/cm^2 (T-score − 3.0 SD, osteoporotic range). Values at the proximal femur were normal. In addition, lumbar column L1–L4 bone texture evaluated by means of the Trabecular Bone Score (TBS) was low at 1.101 (NV > 1.310). A neurological evaluation was performed due to memory complaints and showed a mild cognitive impairment with a Montreal Cognitive Assessment test at 24/30. The brain MRI was normal, but the 18F-FDG positive emission tomography revealed a hypoactivity in the central sulcus region. The neuropsychological evaluation showed executive dysfunction, severe loss in verbal episodic memory, ideomotor apraxia and troubles in facial recognition. These findings were compatible with early signs of fronto-temporal dementia (FTD).

The association of splenomegaly, hepatomegaly, interstitial lung disease, bone involvement, and possible beginning FTD raised the suspicion of a genetic multisystem disorder, and more specifically, of a lysosomal storage disease (LSD). Normal β-glucocerebrosidase activity as measured on peripheral leucocytes excluded Gaucher disease [6]. A bone marrow aspiration revealed

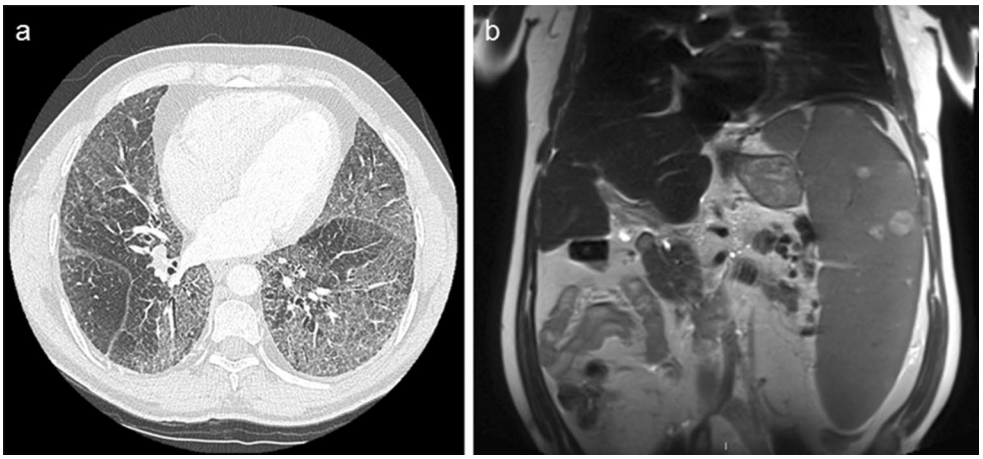

Fig. 1 Radiological finding in Niemann–Pick disease type B. **a** HRCT of the chest showing multifocal areas of ground-glass opacities with mild smooth interlobular septal thickening and intralobular lines (crazy-paving pattern), predominantly located in the lower lobes. **b** T2-weighted coronal magnetic resonance image showing splenomegaly with hyperintense nodules of variable size [25]. *HRCT* high-resolution computed tomography

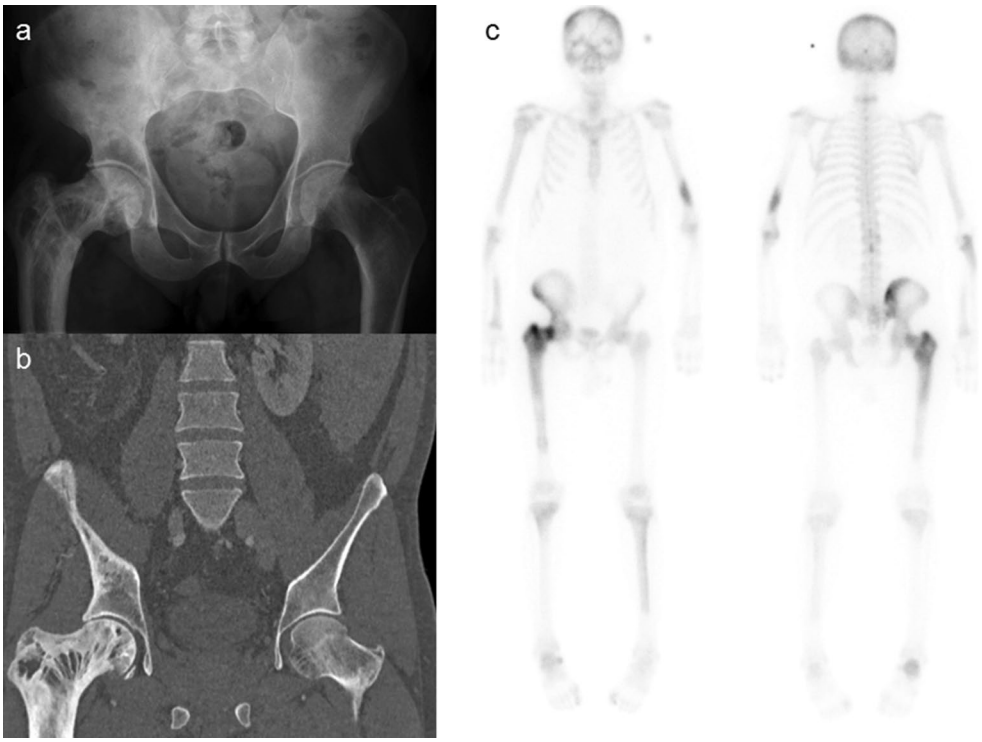

Fig. 2 Radiological finding of Paget's disease of bone. **a** Standard radiography and **b** Coronal CT scan of the pelvis showing heterogeneous lytic and sclerotic lesions with cortico-medullary dedifferentiation, coarse trabeculation, and cortical thickening of the right femur and right iliac bones. **c** Bone scan showing increased uptake in the involved bones. *CT* computerized tomography

foamy "sea-blue histiocytes", strongly suggesting Niemann–Pick disease (NPD) (Fig. 3). Residual acid sphingomyelinase (ASM) activity in cultured skin fibroblasts was less than 10% of controls (5.3%), confirming NPD type B [7]. Molecular analysis was done by next-generation sequencing (NGS) on an Ion S5 system (Thermo Fisher Scientific) using a gene panel for lysosomal diseases. This revealed a homozygous 3 base pair deletion in the exon 6 of the *SMPD1* gene introducing a premature stop codon: c.1829_1831delGCC, p. Arg610del [8].

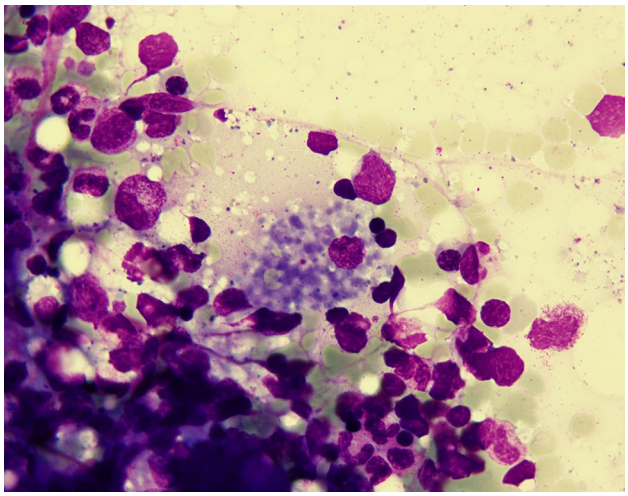

Fig. 3 Bone marrow aspiration finding in Niemann–Pick disease type B. Foamy macrophage histology of Niemann–Pick disease type B

However, the distribution of bone lesions and their heterogeneous uptake was not considered typical for a storage disease and more investigations were undertaken. Bone turnover markers were elevated: bone ALP 176 µg/l (NV 5, 7–32, 9); CTX1 828 ng/l (NV < 704), and P1NP 361 µg/l (NV 15–78). Based on this as well as on radiological and scintigraphy studies, the diagnosis of PDB was considered. Molecular analysis of the patient was done by direct PCR amplification of *SQSTM1* exons from the proband's genomic DNA followed by direct bidirectional Sanger sequencing. This revealed a heterozygous mutation in the exon 8 at position c.1175 (c.1175C > T) in the *SQSTM1* gene which led to the change of Proline with Leucine in codon 392 (p.Pro392Leu). This is a recurrent mutation known to be associated with PDB. Both the *SMPD1* and the *SQSTM1* variants were confirmed by a novel Sanger sequencing in the patient, and shown to be present in both parents at the heterozygous state (*SMPD1*) or present in maternal and absent in paternal DNA (*SQSTM1*). Completion of the family history was significant for the patient's mother reporting chronic bone pain but no fracture; radiographs were not taken, but it seems likely that the mother also has PDB.

In the absence of fractures or local pain, calcium and vitamin D supplementation were prescribed to the patient, without anti-resorptive treatment. Over the following 2 years, he developed progressive respiratory insufficiency requiring supplemental oxygen. Pulmonary function testing revealed decreased lung volume and DLCO (from 50 to 29% of predicted). A therapeutic bronchoalveolar lavage failed to improve his respiratory function. As the patient was not eligible to join the Olipudase® study due to his low platelet count and respiratory insufficiency, nor for lung transplantation, supportive treatment was maintained.

Discussion

In 2017, Posey et al. reported a retrospective analysis of 2076 patients who had been referred for genetic investigations by exome sequencing and in whom a molecular diagnosis had been obtained. Of these patients, 101 (4.9%) were found to have not a single, but rather two to four distinct genetic diagnoses [9]. As discussed in the accompanying editorial, this finding challenges the notion that a genetic investigation is complete after a pathogenic mutation has been identified [10]. Physicians are taught to try and "unify" the diagnosis. For genetic conditions, this means that when mutations in one gene are found, the diagnostic procedure is considered successful and comes to a halt. Even when clinical findings do not entirely match those previously described for the genetic condition, the patient may be thought to have an atypical presentation of the disease. This is true in a large proportion of cases, as exome sequencing has taught us that "atypical" presentations are at least as common as textbook ones; however, the other side of the coin, namely that of multiple genetic diagnoses in a single patient, must also be considered.

In this patient, splenomegaly and sea-blue histiocytes made the diagnosis of Niemann–Pick disease relatively straightforward. Following the biochemical and molecular confirmation, we wondered whether Paget-like bone lesions were a yet under-recognized bone manifestation of adult-onset NPD-B. Bone involvement is frequently observed in LSD due to direct substrate storage, inflammation and other complex alterations of cartilage, bone metabolism and homeostasis [4]. To date, two clinical case reports describe skeletal involvement in NPD-B: a postmenopausal woman with vertebral fractures [11] and a MR low-intensity coarse pattern in the femur of a 62-year-old Caucasian woman [12]. Most pediatric and adult NPD-B patients are at risk for fractures, osteopenia and/or osteoporosis [4]. Finally, NPD-B patients complain of joint or limb pain suggesting that skeletal involvement may be a common feature of NPD-B [13]. However, none of the reports on NPD-B showed Paget-like lesions like those seen in our patient, and the identification of a separate "PDB mutation" allowed us to terminate our struggle to place all findings under a single unifying diagnosis.

PDB is a relatively common skeletal disorder characterized by focal areas of increased and disorganized bone turnover affecting one or more skeletal sites, and inducing abnormal bony architecture, marrow fibrosis, and increased vascularity of bone. Genetic predisposition to PDB has been linked to genes involved in the control of osteoclast differentiation and function, namely mutations in the sequestosome 1 (*SQSTM1*) gene [14]. Although PDB is probably genetically heterogeneous, in some

familial cases of late onset PDB an autosomal dominant pattern of inheritance has been reported [5]. Interestingly, and dramatically, the finding of a known pathogenic mutation in *SQSTM1* not only explained Paget's disease coexisting with NPD-B, but lent further support to the suspected diagnosis of beginning FTD. Indeed, mutations in *SQSTM1* have been reported in association with FTD, possibly because of defective autophagy and protein aggregation [15, 16]. Dysfunctional autophagy receptors might explain the inability to clear aggregates and their presence in neurons of *SQSTM1* mutation carriers. Dysregulation of autophagy is considered to be one of the pathogenic cascades in PDB/FTD [14, 17] but also in several LSDs [18], raising the hypothesis of a common pathogenic mechanism affecting the formation and clearance of misfolded proteins.

Could there be an interaction between the *SQSTM1* and the *SMPD1* mutations? The protein encoded by SMPD1 is a lysosomal acid sphingomyelinase that converts sphingomyelin to ceramide, while SQSTM1 encodes for sequestosome-1, an autophagosome protein that binds other proteins for selective autophagy. Evidence indicates that high sphingomyelin levels such as found in ASM deficiency may induce autophagy dysfunction by impairing autophagolysosomal degradation [19]. It is thus possible that coinheritance of PDB and NPD-B may aggravate the clinical phenotype. In addition, sphingosine-1-phosphate (S1P), a downstream metabolite of ASM activity pathway, is an important mediator of bone metabolism and has a chemotactic effect on osteoclast precursors, and dose-dependent effects on osteoblasts proliferation and differentiation in blood and bone marrow [20–22]. Further studies assessing the level of S1P in samples of NPD-B patients and its impact on autophagy and osteoclast functions could be of interest.

Identification of two different genetic conditions in our patient influenced the choice of treatment. Treatment with bisphosphonates is often considered in PDB patients as it relieves symptoms and may reduce the risk of complications [14]. However, molecules from the amino-bisphosphonates family, although not those licensed, have been shown to be potent inhibitors of ASM in vitro [23, 24]. Therefore, using bisphosphonates in patients with NPD-B could potentially accelerate the disease course. A single case report on pamidronate treatment for severe osteoporosis in a NPD-B patient has been published so far [11]; the reported clinical course does not confirm nor invalidate this hypothesis. If NPD-B and PDB are co-existing, bisphosphonates should be used cautiously and under close follow-up, due to their potential inhibition of residual ASM activity.

In conclusion, by reporting a patient with a multisystemic clinical phenotype caused by a co-occurrence of two distinct genetic conditions, we would like to emphasize the phenomenon of combined monogenic rare diseases in a single patient. While every genetic disease may have atypical presentations, physicians should consider the possibility of an additional diagnosis if the phenotypic features are not clearly explained by the initial monogenic diagnosis. Accurate diagnostic work-up can guide genetic counseling but also lead to better medical management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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