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BRIEF REPORT

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Hematopoietic stem cell transplantation in Niemann–Pick disease type B monitored by chitotriosidase activity

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Abstract

Here, we report a patient with Niemann–Pick disease type B, with early severe onset of disease and pulmonary involvement, treated with hematopoietic stem cell transplant (HSCT) from a bone marrow matched unrelated donor. We confirm that HSCT is feasible and potentially beneficial for patients with severe phenotype. Noteworthy, we discussed the potential usefulness of the activity of peripheral chitotriosidase for the longitudinal evaluation of HSCT success and effectiveness.

KEYWORDS

chitotriosidase activity, hematopoietic stem cell transplantation, Niemann–Pick disease type B

1 | INTRODUCTION

Niemann–Pick disease (NPD) type B is a rare autosomal recessive sphingolipidosis caused by the deficiency of the lysosomal acid sphingomyelinase (ASM; EC 3.1.4.12), which is encoded by the SMPD1 gene.[1] After the neonatal period, increased activity of peripheral chitotriosidase (ChT)—a chitinase synthesized by activated macrophages—might suggest a diagnosis of NPD as it is a marker of disease progression.[2,3] Clinically, NPD type B shows a broad spectrum of manifestations, ranging from onset in infancy with massive hepatosplenomegaly, interstitial lung disease, and growth restriction to later onset of attenuated forms presenting in adulthood with isolated splenomegaly or mild pulmonary reticular fibrosis. Neurological involvement is generally absent.[1,4–6] No specific treatment is currently available. Besides supportive measures, hematopoietic stem cell transplant (HSCT) from matched family donor has been attempted in very few patients with NPD type B.[4,7–11] Only few patients, included in a large cohort of inherited metabolic disorders, underwent umbilical cord blood transplantation.[12] Enzyme replacement therapy with recombinant ASM is under evaluation for milder forms.

Here, we describe a case of a severe, early onset NPD type B patient successfully treated with HSCT from a bone marrow (BM) matched unrelated donor (MUD).

Abbreviations: ASM, acid sphingomyelinase; ATG, antithymocyte globulin; BM, bone marrow; ChT, chitotriosidase; CT, computed tomography; GvHD, graft-versus-host-disease; HSCT, hematopoietic stem cell transplant; MUD, matched unrelated donor; NPD, Niemann–Pick disease

1.1 | Case report

A 3-year-old Caucasian female child referred to our Department presenting with fever, massive hepato-splenomegaly and dyspnea (respiratory rate 48 breaths per minute, O_2 saturation 88%). The patient was born full term after an uncomplicated pregnancy. She had normal growth and development to that point.

The laboratory findings were as follows: RBC 4.39 × 10^{12}/l, hemoglobin 11.4 g/dl, WBC 6.7 × 10^9/l (neutrophils 73%), platelets 134 × 10^9/l. Other findings included persistent hyperferritinemia, increased cholesterol and triglyceride levels, and progressive hypofibrinogenemia.

A chest X-ray revealed increased reticular and nodular interstitial markings. Abdominal ultrasound showed enlarged spleen and enlarged hyperdense liver. A high-resolution computed tomography (CT) scan evidenced severe interstitial lung disease, with diffuse alveolar thickening mostly in the posterior segments. Magnetic resonance imaging of the brain was normal. A BM aspirate was performed and revealed evident signs of hemophagocytosis associated with the presence of multiple sea blue histiocytes (Fig. 1A).

While the clinical scenario was very much suggestive of macrophage activation syndrome, the presence of multiple sea blue histiocytes in the BM and the severe hepatosplenomegaly prompted us to put the suspicion of a storage disease.

Consistent elevation of ChT activity on both peripheral and BM blood was observed (1,052 and 2,462 nM/hr/ml, respectively; normal range 40–350 nM/hr/ml).

The clinical and histological suspicion of early onset NPD type B was confirmed both at biochemical and molecular level, with marked

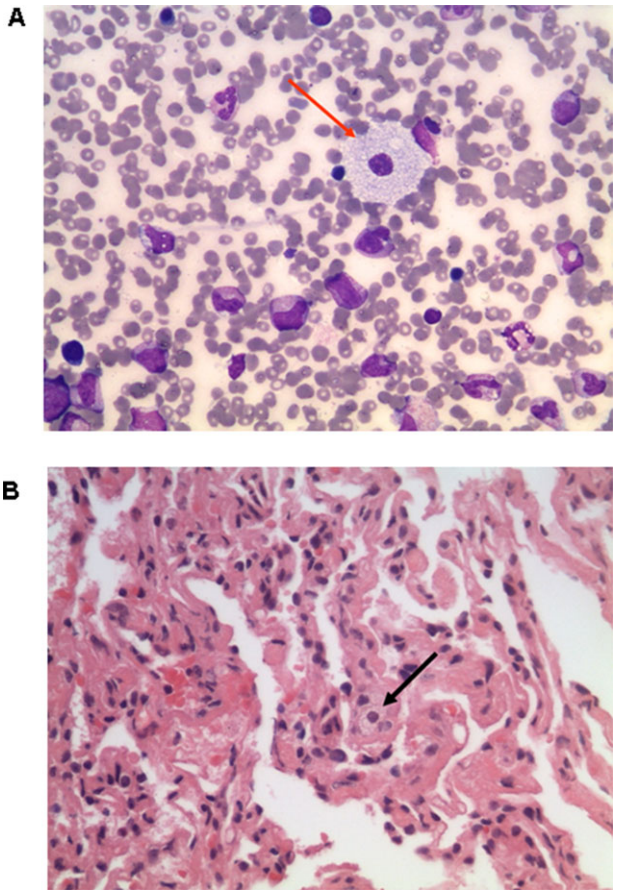

FIGURE 1 (A) Bone marrow aspiration specimen, 400×. The arrow points to a sea blue histiocyte. (B) Lung biopsy specimen, 400×. The arrow points to an interstitial foamy macrophage

reduction of ASM activity on fibroblasts (<1% than normal) and identification of two mutations in the SMPD1 gene (c.[96G > A];[258G > A], p.[W32∗];[W86∗]). The p.W32∗ mutation had previously been found in homozygosity in a patient presenting the less severe type B phenotype.[13] As this mutation introduces a premature stop codon just before the second in frame ATG, it could be supposed that a second initiation codon (ATG33) may be used resulting in the synthesis of a smaller protein still partially active. The p.W86∗ nonsense mutations introduced a premature termination codon, which would lead to a truncated and nonfunctional protein. It is reasonable to hypothesize that this mutation would be related to a severe phenotype.[14]

Given the severity of the clinical picture, the patient was a candidate for HSCT. Institutional informed-consent forms were signed by parents.

The patient received a histocompatible HSCT using BM harvested from fully MUD. Myeloablative therapy was administered with oral busulfan (16 mg/kg), cyclophosphamide (120 mg/kg), and etoposide (30 mg/kg). Antithymocyte globulin, methotrexate 15 mg/m^2 on day + 1 and 10 mg/m^2 on days +3 and + 6, and cyclosporine (3 mg/kg) were used for prophylaxis for graft-versus-host-disease (GvHD).

The patient then received a total of 6.2×10^8/kg nucleated BM cells per kilogram. The total number of CD34$^+$ cells infused was 8.9×10^6/kg.

Initial signs of count recovery (neutrophil count > 500/μl) were seen by day 22. A full donor chimerism (>97% donor) was observed on day 75 and it remained stable thereafter.

HSCT allowed the steady normalization of peripheral ASM activity (2.91 μmol/l/hr, normal range 1.3–21 μmol/l/hr). The longitudinal time course of ChT and ASM after HSCT is shown in Figure 2A.

As posttransplant period was complicated by cutaneous GvHD that was unresponsive to steroids treatment alone, the patient was successfully treated with extracorporeal photoapheresis from day 34.

Seven months after HSCT, the patient developed an acute severe respiratory insufficiency (respiratory rate 60 breaths per minute, O_2 saturation 80%). A chest CT showed pulmonary interstitial reticulo-nodular thickening (Fig. 2B). An H1N1 flu virus infection was detected by real-time PCR following a nasal swab. The peripheral ASM activity was normal, ChT was in progressive reduction, and a full donor chimerism on BM aspirate was confirmed. A lung biopsy showed the presence of interstitial infiltration of foamy macrophages (Fig. 1B).

She was treated with intravenous broad-spectrum antibiotics and intravenous low-dose steroids and she needed continuous noninvasive ventilatory support via high-flow nasal cannula for several weeks.

This respiratory acute complication was then followed by a slow clinical recovery. A second chest CT performed 57 days after the acute episode was consistent with the clinical rescue, showing almost complete regression of parenchymal and interstitial lesions (Fig. 2C).

The normal level of NPD markers (ASM, ChT) and the confirmation of a full donor chimerism supported the diagnosis of an intercurrent infectious episode. The persistence of an interstitial infiltration of foamy macrophages might be explainable by a process of not yet complete clearance of storage cells from visceral organs. Immunosuppressive treatment with cyclosporine was stopped at 12 months after HSCT.

Seven months after the suspension of cyclosporine, the patient developed significant hyperbilirubinemia and elevated liver enzymes. Chronic GvHD[15] of the liver was confirmed by biopsy. Oral tacrolimus was successfully administered and stopped after 18 months.

At present, the child, who is now 8 years old, is doing well 4 years after HSCT and has stable normalization of both peripheral ASM activity and ChT levels (Fig. 2A). Her pulmonary symptoms have improved (respiratory rate 20–25 breaths per minute, O_2 saturation 96–97%) and does not need oxygen therapy. A gradual reduction of hepatosplenomegaly and a significant lowering of both triglyceride and low-density lipoprotein cholesterol levels were also observed. The patient is now attending school at a grade level appropriate for age without any severe long-term neurological impairments.

2 | DISCUSSION

HSCT is a rational therapeutic approach for NPD type B (the nonneuronopathic form of ASM deficiency) whose natural history is characterized by hepatosplenomegaly with progressive hypersplenism, worsening atherogeneic lipid profile, and gradual deterioration in pulmonary functions.[6]

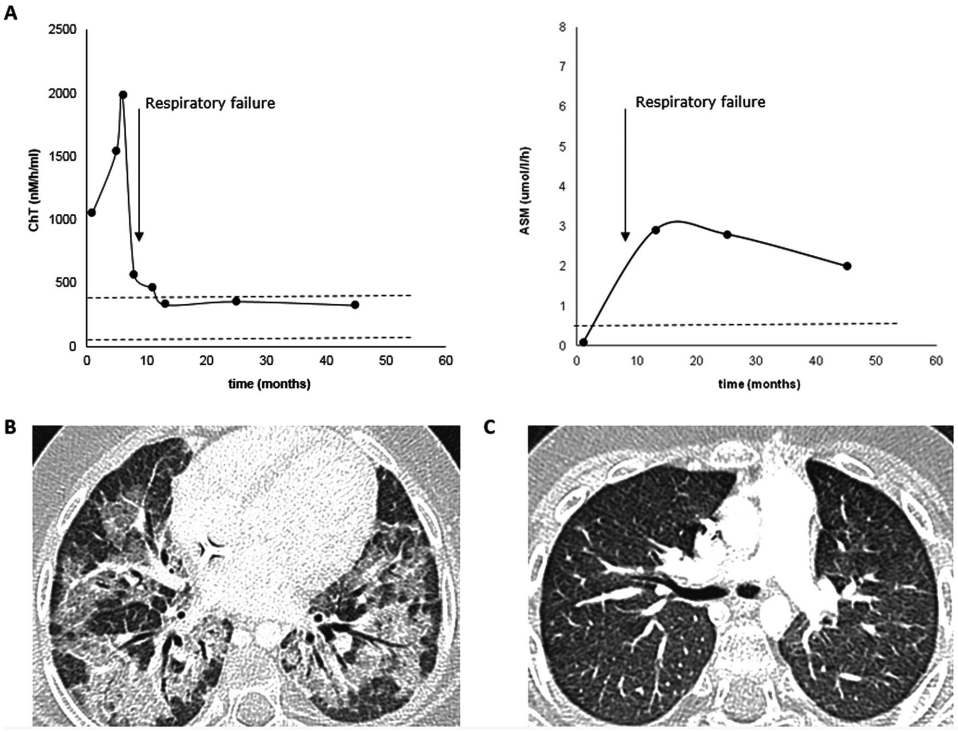

FIGURE 2 (A) Time course of normalization of chitotriosidase (ChT) and lysosomal acid sphingomyelinase (ASM) after allogenic hematopoietic stem cell transplantation (HSCT). ChT normal range 40–350 nM/hr/ml. ASM normal value > 1.3 μmol/l/hr. (B) and (C) Computed tomography (CT) during (B) and after (C) the episode of respiratory insufficiency

To date, only a few patients with NPD type B have been treated with HSCT.[8–12] We have chosen HSCT considering the early severe onset of disease with pulmonary involvement affecting the patient. HSCT improved interstitial lung disease, strictly related to the correction of ASM deficiency. Interestingly, in our patient the normalization of ChT was useful because it suggested that the pulmonary event might be due to an acute infectious event instead of a resurgence of the NP disease.

The persistence of an interstitial infiltration of foamy macrophages might be due to a not yet complete clearance of storage cells from visceral organs. As lung biopsy is invasive, we have not scheduled a second surgical procedure to confirm the probable progressive reduction of the storage cells suggested by the observed clinical benefit of HSCT.

As far as GvHD is concerned, our case also confirms the observations by Orchard and Blazar that ASM deficiency does not protect from GvHD in HSCT recipients with NPD.[16]

In conclusion, taking into account the serious potential sequelae of NP type B disease, HSCT should be considered feasible and potentially beneficial for patients with a severe phenotype. The improvement of outcome results achieved by allogeneic HSCT from unrelated donors in the last decade due to high-resolution HLA-typing and ameliorated management of GvHD means this therapeutic option should not be excluded when an unaffected HLA-matched sibling donor is not available. The role of ChT in NPD patients who underwent HSCT has to be validated in a larger cohort of patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Hollak CE, de Sonnaville ES, Cassiman D, et al. Acid sphingomyelinase (ASM) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. *Mol Genet Metab*. 2012;107:526–533.
2. Wajner A, Michelin K, Burin MG, et al. Biochemical characterization of chitotriosidase enzyme: comparison between normal individuals and patients with Gaucher and with Niemann–Pick diseases. *Clin Biochem*. 2004;37:893–897.
3. Porta F, Pagliardini V, Barbera C, et al. Neonatal chitotriosidase activity is not predictive for Niemann–Pick disease type A/B: implications for newborn screening for lysosomal storage disorders. *Mol Genet Metab*. 2013;108:106.
4. McGovern MM, Wasserstein MP, Giugliani R, et al. A prospective, cross-sectional survey study of the natural history of Niemann–Pick disease type B. *Pediatrics*. 2008;122:e341–e349.
5. Minai OA, Sullivan EJ, Stroller JK. Pulmonary involvement in Niemann–Pick disease: case report and literature review. *Respiratoty Med*. 2000;94:1241–1251.
6. Wasserstein MP, Desnick RJ, Schuchman EH, et al. The natural history of type B Niemann–Pick disease: results from a 10-year longitudinal study. *Pediatrics*. 2004;114:e672–e677.
7. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann–Pick disease. *J Inherit Metab Dis*. 2007;30:654–663.
8. Vellodi A, Hobbs JR, O'Donnell NM, Coulter BS, Hugh-Jones K. Treatment of Niemann–Pick disease type B by allogeneic bone marrow transplantation. *Br Med J*. 1987;28(295):1375–1376.

9. Schneiderman J, Thormann K, Charrow J, Kletzel M. Correction of enzyme levels with allogeneic hematopoeitic progenitor cell transplantation in Niemann–Pick type B. *Pediatr Blood Cancer*. 2007;49:987–989.
10. Victor S, Coulter JB, Besley GT, et al. Niemann–Pick disease: sixteen-year follow-up of allogeneic bone marrow transplantation in a type B variant. *J Inherit Metab Dis*. 2003;26:775–785.
11. Shah AJ, Kapoor N, Crooks GM, et al. Successful hematopoietic stem cell transplantation for Niemann–Pick disease type B. *Pediatrics*. 2005;116:1022–1025.
12. Prasad VK, Mendizabal A, Parikh SH, et al. Unrelated donor umbilical cord blood transplantation for inherited metabolic disorders in 159 pediatric patients from a single center: influence of cellular composition of the graft on transplantation outcomes. *Blood*. 2008;112:2979–2989.
13. Pittis MG, Ricci V, Guerci VI, et al. Acid sphingomyelinase: identification of nine novel mutations among Italian Niemann Pick type B patients and characterization of in vivo functional in-frame start codon. *Hum Mutat*. 2004;24:186–187.
14. Zampieri S, Filocamo M, Pianta A, et al. SMPD1 mutation update: database and comprehensive analysis of published and novel variants. *Hum Mutat*. 2016;37:139–147.
15. Jagasia MH, Greinix HT, Arora M, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2015;21:389–401.
16. Tolar J, Eapen M, Orchard PJ, Blazar BR. Acid sphingomyelinase deficiency does not protect from graft-versus-host disease in transplant recipients with Niemann–Pick disease. *Blood*. 2010;14(115):434–435.

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