Molecular Genetics and Metabolism Reports 25 (2020) 100652

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Short Communication

Allogeneic hematopoietic stem cell transplantation for treating severe lung involvement in Gaucher disease

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ARTICLE INFO

Keywords:
Lysosomal storage disease
Infiltrative lung disease
Glucocerebrosidase

ABSTRACT

Objective: To provide strategies for monitoring and treating severe lung involvement in Gaucher disease.
Study design: We reviewed the chart of a 5-year-old boy who developed rapidly progressive, severe infiltrative lung involvement of Gaucher disease (GD) and improved after allogeneic hematopoietic stem cell transplant (HSCT), along with other case studies reported before December 2019. He was diagnosed with GD (homozygous mutation at c.1448 T > C, p.L483P), and started receiving enzyme replacement therapy (ERT) at 17 months old. He developed respiratory distress symptoms after 45 months of ERT; chest imaging reported diffuse interstitial infiltration of the bilateral lungs and consolidations at the right lungs. Allogeneic HSCT using cells from a matched unrelated donor was performed four months upon progressive respiratory symptoms.
Results: His respiratory symptoms subsided in one month; chest imaging improvement, pulmonary function test improvement, and normalized activity of β-glucocerebrosidase were reported in three months.
Conclusion: This is the first report of a patient who received early and regular ERT but developed severe infiltrative lung involvement and recovered after allogeneic HSCT. Based on study results, we suggest regular chest imaging, even for asymptomatic patients. For patients with severe lung involvement, rapid deterioration, and unresponsive to higher ERT dosages, allogeneic HSCT should be considered.

1. Introduction

Gaucher disease (GD) (OMIM nos. 230800, 231000, and 230900) is an autosomal recessive disorder resulting from mutations in the glucocerebrosidase 1 *(GBA1)* gene located on chromosome 1q21. The deficiency of lysosomal enzyme glucocerebrosidase (GCase) leads to the accumulation of glucocerebroside and other glycolipids within the lysosomes of macrophages, transforming macrophages into storage cells named Gaucher cells. Subsequently, hyperplastic cellular responses and inflammatory responses arise in the surrounding tissues. Gaucher cells mainly infiltrate the spleen, liver, bone marrow, and the nervous system, and also activate a wide spectrum of cytokines that results in bone pain and crises. Less commonly, Gaucher cells also affect the lung [1].

GD is classically divided into three main subtypes according to the presence of neurological involvement, age at determination and progression rate. Currently, GD is viewed as a continuum of phenotypes, and genetic testing is required for diagnosis and treatment planning. Specifically, the combination of four allele variants L483P (previously L444P), 84GG, N409S(N370S), and IVS2, account for 80% of the reported phenotypes worldwide [1].

In all GD types, major clinical manifestations include splenomegaly, hepatomegaly, thrombocytopenia, anemia, osteopenia, bone pain, and bone crises [2]. The initiation of enzyme replacement therapy (ERT) dramatically improved the hematologic and visceral manifestations within the first two years of ERT [2]. Results of a 10-year follow-up in non-splenectomized patients were also significant: increase in hemoglobin levels and platelet count, decrease in liver and spleen volumes, improvement in DXA *Z*-scores, and reduction in bone crises [3].

Pulmonary involvement in Gaucher disease (GD) includes interstitial lung disease, alveolar/lobar consolidation, pulmonary hypertension, and hepatopulmonary syndrome [4]. It is less common than

Abbreviations: GD, Gaucher disease; HSCT, Allogeneic hematopoietic stem cell transplant; ERT, Enzyme replacement therapy; CXR, Chest X-ray; HRCT, High-resolution computed tomography; FVC, Forced vital capacity; FEV, Forced expiratory volume; PEF, Peak expiratory flow; FEF, Forced expiratory flow

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https://doi.org/10.1016/j.ymgmr.2020.100652
Received 20 August 2020; Received in revised form 18 September 2020; Accepted 19 September 2020

visceral, hematologic, and bone manifestations. In type 1 GD, clinically significant lung disease is rare and pulmonary infiltration progresses slow, although it has been reported that 68% of the patients had mild lung function decreases [5,6]. Many GD type 2 and type 3 patients develop infiltrative lung disease over time [7], and 50% of fatal GD type 2 cases are caused by GD-pneumopathy, GD-related aspiration, and aggravation of respiratory conditions [8]. Clinically significant lung involvement also seems more prevalent in homozygous L483P mutation [9,10], and patients with L483P/L483P mutation generally produce more severe early-onset disease that progresses rapidly if untreated [5,11].

Early application of ERT has averted many irreversible complications that are now less common such as; pulmonary hypertension, which is frequently seen in splenectomized patients, and hepatopulmonary syndrome, a complication of long-standing liver disease [12,13]. Infiltrative lung involvement, including interstitial lung diseases and rapidly progressive lung consolidation, is caused by Gaucher cells infiltrating the perivascular, peribronchial, septal regions, and alveolar air spaces [5,14,15]. Currently, the disease course of infiltrative lung involvement is unclear. The treatment effect of ERT in reversing lung disease is generally poor, and its ability to prevent patients from developing lung involvement is unclear. The alternative treatment for GD, Eliglustat, a substrate reduction therapy (SRT), was only indicated for adult patients with GD type 1. Miglustat, another SRT, may have positive results on pulmonary function but failed to show improvement in neurological manifestations [16]. Allogeneic hematopoietic stem cell transplantation(HSCT), the only curative treatment for GD, is effective in alleviating most GD manifestations: improvements in hematological profile, regressing the size of reticuloendothelial organs, reducing skeletal problems, and even arresting neuropsychological deterioration in some [17,18]. Nevertheless, HSCT is less considered as a treatment option for GD type 1 and even GD type 3 because of the substantial risk and the general success of ERT and SRT for controlling the common clinical manifestations of GD. In severe lung involvement of GD which has suboptimal response to ERT and SRT, however, the effect of HSCT has not been well documented, despite that Starer et al. in 1987 discussed a GD type 1 patient whose clinical symptoms subsided and pulmonary infiltrates were cleared in 18 months after allogeneic HSCT [19]. Also, no other published studies have presented the outcome of allogeneic HSCT for GD with severe lung involvement despite regular and early ERT.

Here, we describe the first patient that developed rapidly progressive symptomatic lung involvement while receiving ERT regularly from the age of 17 months. He was previously described in a case report in MGM Reports in 2019 [20], and the later development of ERT-resistant lung disease treated successfully with allogeneic HSCT will be discussed in this report. We also describe a younger brother of the patient with GD who was started on ERT earlier and in higher dose than his brother and in whom, despite the presence of radiologic lung abnormalities continues free of respiratory symptoms.

2. Methods

We assessed two GD brothers (patients A and B) with biallelic mutations at c.1448 T > C, p.L483P, who developed infiltrative lung disease while being treated with ERT early and regularly. We compared their normalized hemoglobin and platelet levels, growth development percentile (before the HSCT of patient A who developed severe lung involvement), liver, and spleen sizes. We also evaluated the lung biopsy pathology, follow-up chest X-ray (CXR), and high-resolution computed tomography (HRCT) images. We reviewed and summarized outcome studies before October 2019 of all patients with GD infiltrative lung disease, including interstitial and alveolar involvement, who had been treated with ERT. The review was based on the search through PubMed with the query “Gaucher disease AND pulmonary” and references in retrieved published studies, with the exclusion of patients reported to be GD type 2.

3. Results

As previously reported, patient A was diagnosed with Gaucher disease at the age of 17 months, with a genetic study showing homozygous mutation at c.1448 T > C, p.L483P. He initially presented with hepatosplenomegaly, anemia, thrombocytopenia, and delayed developmental milestones. A leukocyte enzyme assay showed decreased β-glucocerebrosidase activity (1.5 μmol/L/h; reference, > 7.5 μmol/L/h). The bone marrow cytology revealed the typical feature of wrinkled-paper cytoplasm in CD68+ histiocytes.

After six months of ERT (imiglucerase 60 IU/kg) given every two weeks, his clinical signs and lab data improved: decrease spleen volume (24.3 to 8 times the normal spleen volume by age), decreased liver volume (3.9 to 2.3 times the normal liver volume by age), increased hemoglobin (8.8 g/dL to 11.6 g/dL), increased platelet count (85,000 /μL to 118,000 /μL), and increased body weight from < 3rd percentile to the 15–50 percentile range. The repeated bone marrow smear revealed restoration of cellularity and moderately decreased infiltration of Gaucher cells. No neurological signs were observed at that time.

At the 20th month of ERT when he was 3 years 1 month old, a regular abdominal Magnetic Resonance Imaging (MRI) reported a 3.5 × 2.3 cm hypointense lobulated mass at liver S5 and S6 under T1 weighted MRI scan, and clustered enlarged lymph nodes at the mesenteric and inguinal regions. The repeated bone marrow examination showed no evidence of a concurrent hematologic malignancy. The pediatric surgeon suggested a liver wedge resection of the S7 and S8 segment, and lymph node sampling and the pathology report identified Gaucheromas and Gaucher cell infiltrated lymphadenopathy. Upon diagnosis of Gaucheroma, the ERT dosage was doubled to 120 IU/kg/2 weeks. After eight months of ERT 120 IU/kg/2 weeks, all Gaucheromas remained the same size and we reverted to the dosage of 60 IU/kg/2 weeks, according to the reimbursement policy of National Health Insurance in Taiwan.

Unfortunately, at the age of 5 years 2 months, after receiving 45 months of ERT treatment, he presented with mild tachypnea and persistent productive night cough. His body weight also dropped below the 15th percentile. CXR showed diffuse reticular interstitial infiltration over both lung fields and consolidative patches over the right lung field and left lower lung field (Fig. 1. A-2). He received Augmentin for a positive urine streptococcus antigen. Bronchoalveolar lavage by flexible bronchoscopy was completed to rule out Gaucher disease with pulmonary involvement, and the cytology study of the lavage was negative for Gaucher cells. However, the disease progresses rapidly in subsequent months (Fig. 1. A-3). Pulmonary function tests reported moderate restrictive lung disease (FVC 53.1%, FEV1 53%, PEF 32.7%, FEF25-75% 35.9%). The HRCT image displayed diffuse interstitial

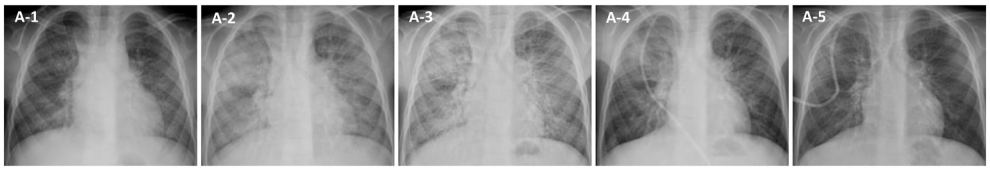

Fig. 1. CXR of patient A.
A-1: Two years before the discovery of lung involvement.
A-2: Discovery of lung involvement.
A-3: Three months after the discovery of lung involvement.
A-4: One month after allogeneic HSCT.
A-5: Three months after allogeneic HSCT.

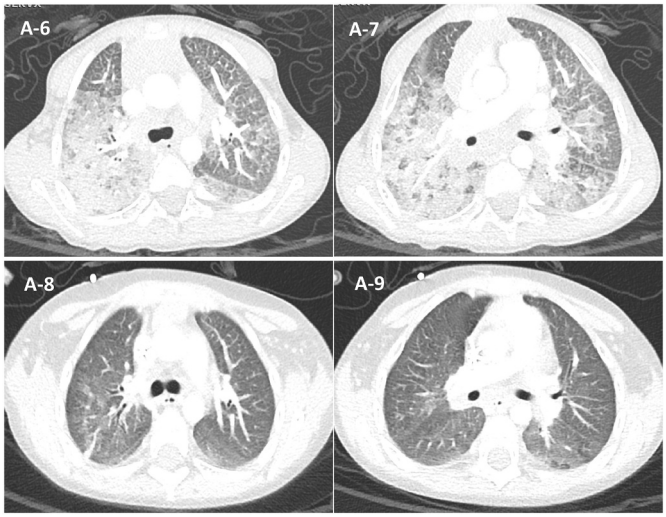

Fig. 2. Chest CT of patient A.
A-6, A-7: Discovery of infiltrative lung involvement.
Diffuse interstitial infiltration at bilateral lungs, with geographic ground glass opacities at bilateral lungs, consolidations mainly at RUL and RLL, and thickening of bronchovascular bundle, interlobar fissure at bilateral lungs. Infiltrative soft tissue lesions at right upper paratrachea, bilateral lower paratrachea, prevascular space, subcarina, AP window, bilateral pulmonary hilum, paraesophageal space, and along the proximal bronchovascular bundle.

infiltration at bilateral lungs with geographic ground-glass opacities and thickening of the bronchovascular bundle and interlobar fissure, and also consolidations mainly at the right upper and lower lungs (Fig. 2. A-6 and A-7). Therefore, a right lower lung wedge biopsy resection was performed, and the pathology report indicated an accumulation of histiocytes in alveolar spaces as well as in interstitium connective tissue, compatible with pulmonary involvement of Gaucher disease. The histiocytes contained pale to lightly eosinophilic cytoplasm with a wrinkled-paper appearance and were immunoreactive for CD68-PGM1 and CD163, and positive with Periodic acid–Schiff stain (PAS) (Fig. 3.). Four months after pulmonary involvement was discovered, allogeneic HSCT using the bone marrow from a 10/10 HLA-matched unrelated donor was performed to control the accelerated deterioration of the lung (Fig. 1., A-2 to A-3). He was conditioned with a myeloablative chemotherapy regimen of busulfan, cyclophosphamide, antithymocyte globulin, cyclosporin A, and short-course methotrexate, which were used as graft-versus-host disease (GVHD) prophylaxis. Neutrophils and platelets were grafted on day 16 and day 30, respectively. Despite gut GVHD and Cytomegalovirus (CMV) antigenemia complications, which resolved after steroid and anti-viral agents usage, the intractable cough and shortness of breath dramatically subsided one month after allogeneic HSCT, while pulmonary alveolar infiltration and ground-glass opacity remarkably improved in three months (Fig. 1., CXR A-4 to A-5). However, the gaucheroma in liver remained the same size. No CNS involvement was observed. Pulmonary function tests improved significantly seven months post-HSCT, with the following results reported: FVC 53.1% ➔ 71.2%, FEV1 53% ➔ 64%, PEF 32.7% ➔ 42.1%, FEF25-75% 35.9% ➔ 40.5%. β-glucocerebrosidase (acid beta-D-glucosidase, ABG) levels also confirmed that disease activity had markedly decreased: 0.42 μmol/L/h before HSCT, and 33.01 μmol/L/h two months after HSCT (reference range: > 7.5 μmol/L/h). The Lyso GL1 level was 100 ng/ml at the 50th month of ERT, and was 35 ng/ml eight months after HSCT (reference range: < 1.0 ng/ml).

Patient B, the younger brother of patient A, was also found to have a

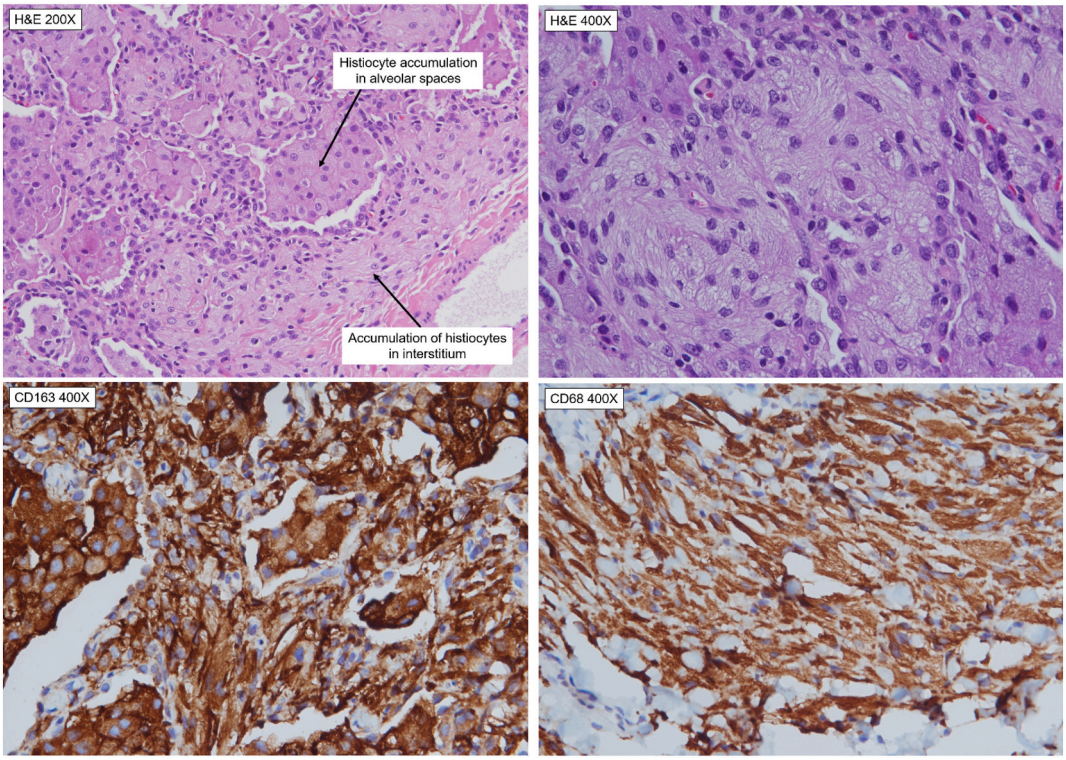

Fig. 3. The lung tissue from open biopsy showed accumulation of histiocytes in alveolar spaces as well as in interstitium connective tissue. The histiocytes contain pale to lightly eosinophilic cytoplasm with wrinkled-paper appearance. The histiocytes are immunoreactive for CD68-PGM1 and CD163 and positive with PAS.
1. H&E staining 200×: accumulation of histiocytes in the alveolar spaces and interstitium.
2. H&E staining 400×: accumulation of histiocytes in the alveolar spaces and interstitium.
3. CD163 400×: positive.
4. CD68 400×: positive.

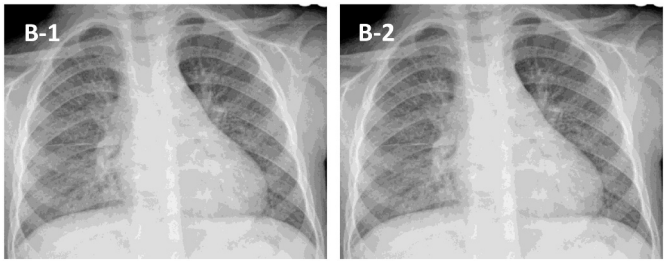

Fig. 4. CXR of patient B.
B-1: Lung involvement found on the image with no respiratory symptoms after 30 months of ERT (60 IU/kg/2 weeks). ERT dosage was then increased to 100 IU/kg/2 weeks. Reticular infiltration over bilateral lung fields, with increased perihilar infiltration and suspicious consolidative patchy over bilateral lower lung fields.
B-2: 11 months after treatment with higher dose ERT (100 IU/kg/2 weeks). Patient B still presented with no respiratory symptoms and normal pulmonary function tests, radiologic findings were mildly improved. Increased interstitial infiltration noted over the bilateral lung field, with prominent pulmonary vasculature.

homozygous mutation of L483P at gestational age 19 weeks by amniocentesis when his elder brother was diagnosed with Gaucher disease. A leukocyte enzyme assay also showed a decreased β-glucocerebrosidase activity of 0.01 μM/L/h after birth. His hematologic profile was normal at five months of age, but hemoglobin 6.6 g/dl and platelet count 104,000 /μL were reported at nine months old (normal range: hemoglobin > 9.5 g/dl, platelet count > 150,000 /μL). ERT was started promptly thereafter.

At the 30th month of ERT when he was 3 years and 5 months old, his CXR showed reticular infiltration over bilateral lung fields, with increased perihilar infiltration and suspicious consolidative patchy over bilateral lower lung fields (Fig. 4. B-1). HRCT reported peribronchial consolidations and opacities at the posterior segment of right upper lung (Fig. 5. B-3 and B-4). Abdominal MRI reported hepatomegaly and splenomegaly, but no gaucheroma was evident. No neurological signs were observed. Thus, we increased the ERT dosage to 100 IU/kg/2 weeks, and his 11-month follow-up CXR showed mild regression in interstitial infiltration (Fig. 4. B-2). Throughout the treatment course, he denied any respiratory symptoms and had normal pulmonary function tests (FVC 97.3%, FEV1 96.6%, FEV 0.5/FVC % = 95.97%).

4. Discussion

This is the first GD patient who received early and regular treatment with the standard ERT dose and still developed a rapidly progressive severe infiltrative lung disease that resolved completely after successful allogeneic HSCT from a matched unrelated donor.

We also reviewed GD patients with infiltrative lung disease before October 2019. A synopsis of all patients who received ERT, excluding those reported to be GD type 2 is presented in Table 1 [21–23].

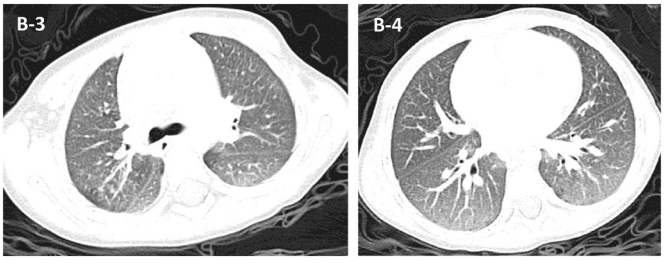

Fig. 5. Chest CT of patient B, 1 month after lung involvement was discovered on CXR.
B-3, B-4: Peribronchial consolidations and opacities at the posterior segment of RUL. Confluent soft tissue nodules at subcarina, bilateral pulmonary hilum, interlobar space/proximal bronchovascular bundle, and retroperitoneum, mesentery root.

ERT effects of the GD type 1 patients that underwent splenectomy varied [24–28]. The 19 non-splenectomized patients who were asymptomatic but revealed infiltrative findings on CXR or HRCT remained stable both clinically and radiologically with ERT treatment in the follow-up time up to eight years, regardless of prior-ERT receipt [13,29–31]. Among symptomatic non-splenectomized patients that started ERT after lung involvement was diagnosed, seven reported stable disease condition or partial improvements with ERT [13,32,33], and only one patient had disease progression [32]. Khalifa et al. reported seven symptomatic patients and suggested initial improvement by increasing dosage to 120 U/kg/2 weeks, although the commencement of ERT before lung involvement was not reported in the paper [34]. The three symptomatic patients who developed lung involvement while receiving ERT, however, reported deteriorated pulmonary function with ERT and one of them died after a year [35,36].

Previous research had suspected poorer accessibility of the infused enzyme to lungs according to autopsy findings in some patients. Burrow et al. reported a 12.5-year-old GD type 3 patient with 11 years of ERT whose autopsy revealed clusters of macrophages and very elevated glucosylceramide (GluCer) and glucosylsphingosine (GluS) levels in the lungs and lymph nodes, while the liver and spleen were clear of storage cells and had nearly normal GluCer and GluS levels [36]. Most autopsy cases in pathological studies reported Gaucher cells in the interstitial tissue and alveoli lumen, including patients who received enzyme therapy with relative systemic efficacy [8]. A study with a GD type 1 mouse model also reported a decrease from pre-ERT GL-1 levels in liver, spleen and lung of 80%, 60%, and 30% respectively. Thus, the lung response was less robust than in either liver or spleen. Additional deployment of an experimental SRT following ERT markedly enhanced the response in lung [37].

The effectiveness of ERT in the lungs should be further studied since there are symptomatic patients that developed infiltrative lung disease while receiving ERT, and some deteriorated rapidly even with increased ERT dosages. It would also be worthwhile to research ERT's pharmacologic mechanism and clarify the turnover of exogenous enzyme and the residual catalytic activity of unstable enzyme variants in the lung [5,25]. Zimran et al. also recommended future improvements in ERT, such as increasing delivery to the storage cells, blocking enzymes from being diverted to other cells, and increasing longevity of enzymes [38]. Additionally, since many patients possessed at least one L483P mutation, we suggest that future studies identify genetic, ethnic, and environmental factors to advance the treatment consensus for GD infiltrative lung diseases, especially symptomatic and fast-deteriorating infiltrative lung involvement, for which further evaluation and longer follow-up will be needed.

Based on our patient, we suggest that allogeneic HSCT should be considered as a treatment option for patients with rapidly progressive, severe infiltrative lung involvement who have already received standard or higher doses of ERT.

Most importantly, it might be helpful to regularly follow up lung image in GD patients, possibly twice a year, regardless of the presence of clinical symptoms or signs. The previous reports show that patients without respiratory symptoms remained clinically stable for years, while symptomatic patients might have accelerated deterioration of lung involvement even when treated with ERT and subsequently develop a lethal condition within months. The presence of lung imaging and histological changes in the lung would guide medical providers to proactively intervene with alternate treatments.

5. Conclusions

This is the first reported patient who received early and regular ERT but still developed severe infiltrative lung involvement that was controlled after allogeneic HSCT. Early and regular ERT still has some

Table 1
GD patients with infiltrative lung involvement that received ERT (excluding Type 2 GD).

Author	Case numbers	Type*	Genetic mutation	Ethnicity/ country*****	splenectomy	ERT before ILD	Respiratory symptoms	Post ERT effects	Follow-up time on ERT	Age at end of follow-up
Beutler et al., [24]	2	1	–	Ashkenazi Jewish	Y	N	Y	Modest improvement of pulmonary function (rest and exercise arterial oxygen saturation)	Up to 13 months	30 y, 45 y
Fallet et al., [25]	1	1	–	Hispanic	Y	N	Y	No improvement, patient died	8 months	12 y
Pastores et al., [26]	3	1	N409S/84GG and unknown	USA	Y	N	Y	No improvement in pulmonary function (static and dynamic lung volumes, diffusion capacity, and arterial oxygen saturation)	6 to 12 months	12 y, 38 y, 52 y
Banjar et al., [27]	1	1	–	Saudi Arabia	Y	N	Y	Improved, weaned off oxygen in 6 months and CXR cleared of bilateral infiltrates; however, recurred due to stopping ERT in 2 months, and improved again with ERT	3 years	8 y
Martinez Odrizola et al., [28]	1	1	N409S/D55	Caucasian	Y	N	Y	Dyspnea improved and DLCO increased, pulmonary hypertension persisted	18 months	29 y
Banjar et al., [32]	4	1 & 3	–	Saudi Arabia	Not reported	N	Y	2 (type 3): Normal ABG and complete resolution on image, 1 (type 3): Improved, but recurred after ERT discontinuation, 1 (type 1): Progressed	2.5 to 3.5 years	4.5 y to 7.3 y
Versteegh et al., [22]	1	1	–	Belgium	N	N	N	Persistent interstitial pattern on image with no clinical signs	2.75 years	6 y
Altarescu et al., [29]	14	3	Mostly L483P/ L483P	****	Some (little, before enrollment)	Some	N	Remained stable, neither prevented nor reversed, in CXR or HRCT. No patient developed clinical respiratory difficulties.	2 to 8 years (median 3.5y)	4 y to 37 y
Goitein et al., [13]	2	–	L483P/L483P	Arab	N	N	Y	Stable condition or partial improvement in CXR and HRCT, but no complete normalization. PFT deteriorated in one and air-trapping in another	8.5 and 4.8 years	10.8 y, 7.2 y
	1	–	L483P/L483P	Arab	N	N	N	More prominent opacities in HRCT on ERT year 5, but remained stable in HRCT on ERT year 7	6.5 years	12.3 y
Lee et al., [30]	1	–	L483P/L483P	Hong Kong	N	Y	N	Complete resolution of ground glass appearance with minimal interlobular thickening on HRCT (after increasing dosage to 100 U/kg/2 weeks)	2.75 years	5.75 y
Miller et al., [33]	2	1	N409S/84GG	Jewish	N	N	Y	Improvement in dyspnea and reticular infiltrates, but no improvement in pulmonary function, pulmonary artery pressure or saturation	6 to 12 months	37 y, 40 y
Goker-Alpan et al., [21]	10	1 & 3	L483P/L483P	USA	N	N/A**	–	No mortality, did not mention pulmonary issues	Up to 8 years	3 y to 21 y
Brunel-Guitton et al., [35]	1	–	L483P/L483P	Canada	N	Y	Y	Deterioration, abnormal PFT and poor functional performance (developed during highest initiation and maintenance dosage)	Median 10 years (2–16 years)**	***
Khalifa et al., [34]	7	–	various	Eygpt	Not clearly reported	N/A**	Y	Initial improvement (after increasing dosage to 120 U/kg/ 2 weeks)	Within 24 months	2 y to 18 y
Djordjević et al., [31]	1	–	L483P/L483P	Serbia	N	Y	N	No change in PFT, no progression in HRCT	7.5 years	9.5 y
Burrow et al., [36]	1	3	K79N/L483P, A456P, D409H	Caucasian	N	Y	Y	Progression, patient died	11.5 years	12.5 y
Kurolap et al., [23]	1	3c	–	Israel	N	Discontinued	Y	Died of cardia arrest	12 years	20 y
Patient A	1	–	L483P/L483P	Taiwan	N	Y	Y	Rapid progression clinically and by CXR (developed during ERT 120 U/kg/2 weeks), resolved after allogenic HSCT	4.75 years	6 y
Patient B	1	–	L483P/L483P	Taiwan	N	Y	N	Normal PFT, No respiratory symptoms Mild regression in interstitial infiltration on CXR (after increasing dosage to 100 U/kg/2 weeks for 11 months)	3.33 years	4.3 y

* Only included types reported by the author.
** Not provided for the patient alone.
*** Age at initiation of treatment: median 5.7 years (1.5–10.8 years), not provided for the patient alone.
**** African American, White, Hispanic.
***** If ethnicity not reported, we reported the country of the institute.

limitations in controlling the infiltrative lung involvement of Gaucher disease. Based on the experiences of our patients and literature review, regular chest imaging follow up for both symptomatic and asymptomatic patients, possibly biannual chest X-rays, might be helpful for Gaucher disease management. Additionally, for patients with severe rapidly deteriorating lung involvement, allogeneic HSCT might be a useful consideration to alleviate this severe condition.

Data sharing statements

Individual participant will data be available. All of the individual participant data collected, after deidentification, will be shared with researchers who provide a methodologically sound proposal. Proposals should be directed to pum_chia@yahoo.com.tw.

A-8, A-9: 7 months after HSCT. Significant regression.

Acknowledgement

Taipei Veterans General Hospital, Grant/Award Number: VGH-109-B-042. Ministry of Science and Technology, Grant/Award Number: 109-2314-B-075-063-.

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