Case report

Lessons from lung transplantation: Cause for Redefining the Pathophysiology of Pulmonary Hypertension in Gaucher Disease

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ABSTRACT

Background: Gaucher disease type 1 (GD1) is a lysosomal storage disease rarely resulting in end stage pulmonary hypertension (PH) and interstitial lung disease. There have only been two previous case reports of patients with GD1 receiving lung transplants.

Case presentation: We report a case of successful bilateral sequential lung transplantation in a patient with end-stage GD1-related PH. Prior to transplant, the patient was on enzyme replacement therapy with imiglucerase and pulmonary vasodilator therapy with bosentan, sildenafil and epoprostenol. The patient had pre-transplant comorbidities of prior splenectomy and osteopenia. She underwent bilateral sequential lung transplantation with basiliximab, methylprednisolone and mycophenolate mofetil induction. Her explanted lungs demonstrated severe pulmonary arterial hypertensive changes, but no Gaucher cells. She was maintained on MMF, tacrolimus, prednisone, imiglucerase and warfarin post-transplant. Her post-transplant course was complicated by hemorrhagic shock, prolonged support with extracorporeal membrane oxygenation, and acute renal failure requiring dialysis. Despite these complications, the patient was discharged and is doing well nine months post-transplantation.

Conclusions: This is one of only three reported cases of lung transplantation in patients with GD1. Each case has involved previously splenectomised, female patients with GD1. This is the first report to transplant a patient with severe PH and no pulmonary parenchymal disease. As evidenced in our patient, long term treatment with imiglucerase may eliminate the Gaucher cells in the lungs. The PH in these patients is most consistent with pulmonary arterial hypertension, raising the question of whether this should be reclassified as WHO Group 1 PH.

1. Introduction

Gaucher disease is an autosomal recessive inherited disorder that is the most common lysosomal storage disease, affecting approximately 1/40,000 live births [1]. The three variants of the disease are characterized by deficient activity of the lysosomal enzyme, glucocerebroside. This results in the accumulation of its substrate, glucosylceramide, in lysosomes of macrophages, predominately in the bone marrow, liver and spleen [2]. Gaucher disease type 1 (GD1) is the most common variant, especially in patients of Ashkenazi Jewish descent [3].

Pulmonary involvement in GD1 can be characterized by interstitial lung disease (ILD) and/or pulmonary hypertension (PH) [1,4]. PH is present in up to 30% of untreated GD1 patients, and 7% of patients receiving enzyme replacement therapy (ERT) [5]. The majority of PH in GD1 patients is seen in splenectomised, female patients, and most cases are responsive to treatment with ERT [5,6]. The patient highlighted in this case was previously included in a series of GD1 patients with PH [5].

Treatment of GD1 with end-stage pulmonary manifestations by lung transplantation has been reported in two previous cases. Ours is the first reported case of lung transplantation in a patient with GD1 for severe PH without pulmonary parenchymal involvement. We also analyze

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Abbreviations

(DLCO) Diffusion capacity for carbon monoxide
(ERT) enzyme replacement therapy
(FEV1) forced expiratory volume in 1 second
(FVC) forced vital capacity
(GD1) Gaucher disease type 1
(ILD) interstitial lung disease
(MMF) mycophenolate mofetil
(RVSP) right ventricular systolic pressure
(PAH) pulmonary arterial hypertension
(PH) pulmonary hypertension
(VA-ECMO) venoarterial extracorporeal membrane oxygenation
(VV-ECMO) venovenous extracorporeal membrane oxygenation

Disease-specific concerns for transplant in these patients, including the risk of GD1 pulmonary disease recurrence, immunosuppression in splenectomised patients, and the risk of liver and bone involvement in GD1.

1.1. Case presentation

Our patient was initially diagnosed with GD1 thirty-six years prior to transplant at age 14 when she presented with splenomegaly and thrombocytopenia. She was treated with a splenectomy, and the diagnosis of GD1 was confirmed with enzymology and genotyping (N370S/F417V). This genotyping also confirmed the absence of any pulmonary arterial hypertension (PAH)-related genes. She was then lost to follow-up, but re-presented in 2000 at age 33 with dyspnea and was found to have severe PH. Treatment with imiglucerase (Cerezyme, Sanofi Genzyme, 45U/kg IV q2weeks), IV epoprostenol (Flolan®, GSK Canada, 92ng/kg/min), and warfarin was initiated. This was followed by addition of bosentan (125 mg PO BID) in 2006, and sildenafil (25 mg PO TID) in 2008. Flolan® was eventually transitioned to a thermostable formulation of IV epoprostenol (Caripul®, Actelion Pharmaceuticals Canada, 88ng/kg/min). She was also managed for her comorbidities of GD1-associated osteopenia and gastroesophageal reflux.

The patient was referred for evaluation for lung transplantation at age 34 in 2001. She did not require transplantation at that time as she initially had a dramatic clinical response to her PH therapy. After a period with stable cardiopulmonary hemodynamics, her functional status worsened, and she progressed to require 3L of oxygen continuously (Fig. 1). Although her right ventricular systolic pressure (RVSP) from transthoracic echocardiography remained relatively stable, her right ventricular systolic function deteriorated, and she developed paradoxical septal motion with bowing into her left ventricle. As a result of this progression, she was actively listed for lung transplantation in 2016.

The patient's last pre-transplant forced vital capacity (FVC) was 1.90L (68% predicted), forced expiratory volume in 1 second (FEV1) 1.23L (52% predicted), and diffusion capacity for carbon monoxide (DLCO) 20.50mL/min/mmHg (107% predicted). Imaging demonstrated no evidence of interstitial lung disease. Her last right heart catheterization 3 months prior to transplant demonstrated a mean pulmonary artery pressure of 62 mmHg, a pulmonary vascular resistance of 20.4 Wood units (increased from 11.2 Woods units 41 months previously), and a Fick cardiac output of 2.4L/min (decreased from 5.0L/min 41 months previously).

Following active listing for transplant, the patient had three admissions for right heart failure and volume overload requiring IV diuresis. Computed tomography pulmonary embolism protocol did not show any evidence of pulmonary embolus but showed new increased interstitial markings in the lung parenchyma consistent with congestive heart failure (Fig. 2). Her condition worsened in 2018 and she was admitted to the critical care unit for vasopressor and inotrope therapy for two weeks until an appropriate donor became available. Her lung allocation score at this time was 45.9. She underwent a bilateral sequential lung transplantation and during the procedure required venoarterial extracorporeal membrane oxygenation (VA-ECMO). There was a size discrepancy with a large donor and a small recipient, so the patient received a left upper lobar transplant and a right lung transplant with a wedge resection of a portion of consolidated donor right lower lobe. The procedure was complicated by significant bleeding requiring massive transfusions and return to the OR for hemostasis.

The explanted lungs demonstrated severe pulmonary arterial hypertensive changes, including intimal proliferation, plexiform and angiomatoid lesions (Fig. 3). There was also patchy bronchiolitis and pneumonitis, potentially reflecting microaspiration, mild infection or drug reaction, but there was no evidence of interstitial fibrosis. The lungs did not demonstrate any pathognomonic features of Gaucher disease, such as filling of the alveolar spaces with Gaucher macrophages, accumulation of Gaucher cells in the alveolar septae and capillaries or perilymphatic infiltration of Gaucher cells. There was also no bone marrow emboli in the pulmonary capillaries, a finding that has rarely been described in patients with GD1 and PH [7,8]. The explant pathology in our patient was typical for that seen in patients with WHO PH group 1 PAH.

Her post-transplant course was complicated by prolonged support with initially veno-arterial (VA)- then venovenous-ECMO (VV-ECMO). After weaning from VV-ECMO, she required a prolonged period of ventilation, and as a result received a tracheostomy three weeks following her transplant. She was successfully decannulated three weeks later. As a result of hemorrhagic shock, the patient developed acute tubular necrosis, requiring renal replacement therapy.

Eight months post-transplant, the patient remains dialysis-dependent with oliguria. Her lung function continues to improve eight months post-transplant with an FVC of 1.80L (63% predicted) and FEV1 of 1.47L (62% predicted). Her restrictive physiology is thought to be related to the donor lung resections and post-transplant hemorhoraces resulting in chronic pleural disease. Her follow-up transbronchial biopsies and bronchoalveolar lavage demonstrate no evidence of acute rejection or infection. She is currently being maintained on immunosuppression with MMF, tacrolimus and prednisone, while continuing her ERT with imiglucerase and anticoagulation with warfarin.

2. Discussion

There have only been two previous reports of lung transplantation...
in patients with GD1 [9,10]. The first was in a 10 year old GD1 patient with extensive ILD, previous bronchoalveolar lavage with evidence of Gaucher cells, and pulmonary hypertensive crisis [10]. The second case was in a patient transplanted at age 49 for severe PH and fibrotic ILD [9]. In both cases, the patients were female, had been treated with ERT, and had undergone splenectomy prior to developing end-stage pulmonary disease. Ours is the first case of a lung transplant in a GD1 patient with severe PH, but without significant pulmonary parenchymal disease.

Pulmonary vascular disease in GD1 is more common than previously recognized, affecting up to 30% of untreated patients and approximately 7% of patients treated with ERT [5]. The PH seen in GD1 is typically mild-to-moderate in severity, but end-stage PH occurs in approximately 1% of patients with GD1 [6]. PH in GD1 has been classified into WHO Group 5, for unclear or multifactorial mechanisms [11]. The classic pathophysiologic explanation for PH in GD1 is that Gaucher cells deposit in the pulmonary parenchyma and capillaries, thus obstructing blood flow [8,12]. However, severe PH in GD1 has been described with little-to-no evidence of Gaucher cells within the lungs [2,13]. The impact of long-term ERT on the presence of Gaucher cells in the lungs is unclear, although this treatment may explain the absence of these cells in the explants from our patient. Other proposed mechanisms of PH include plugging of pulmonary capillaries with bone marrow emboli [7,8], post-splenectomy PH [5], and PH via the hepatopulmonary syndrome in patients with GD1-associated liver disease [6]. Analysis of BMPR2 and ALK1 coding regions did not disclose a role for these modifier genes in GD1 [6].

Splenectomy has been shown to be a primary factor in the development of PH in GD1 [5,6]. The proposed mechanism of PH following splenectomy is thought to relate to hypercoagulability from lack of splenic clearance of platelets and megakaryocytes. This results in deposition of megakaryocytes and macrophages within the pulmonary vasculature, leading to development of proximal thrombi (i.e. chronic thromboembolic pulmonary hypertension phenotype) or distal thrombi manifesting as a plexogenic arteriopathy (i.e. pulmonary arterial hypertension phenotype) [5,14].

Asplenia is also an important post-transplant consideration. Asplenic solid organ transplant recipients are more likely to experience bacterial pneumonias post-transplant [15]. However, these patients may be at a lower risk of antibody-mediated rejection (AMR). Splenectomy has previously been used as a salvage treatment for AMR in kidney transplantation [16], and it has also been used to facilitate ABO-incompatible kidney transplants [17]. No studies have evaluated the mortality impact of splenectomy in lung transplant recipients.

Although it has previously been mentioned as a theoretical concern [9], the risk of recurrence of PH related to GD1 in transplanted lungs should be extremely low if the patient remains on ERT. Patients treated with ERT have a much lower likelihood of developing PH or other pulmonary manifestations than those without ERT [5]. As evidenced in our patient, long term treatment with imiglucerase may completely eliminate the Gaucher cells in the lungs, although it will not alleviate the thrombogenic risk associated with splenectomy. Ongoing ERT post-transplant and should minimize any risk of post-transplant pulmonary and systemic complications of GD1.

3. Conclusions

Our case, in conjunction with the two previous cases of lung transplantation in GD1, demonstrates the efficacy of this treatment for patients with end-stage pulmonary disease from this condition, although reported follow-up is limited. Given the success and availability of ERT that has reduced the need for splenectomy, end stage pulmonary disease in GD1 may become less frequent. Nonetheless, 7% of patients with GD1 may develop severe PH despite adequate ERT. This is most common in female, splenectomised patients. As long as ERT is continued in the post-transplant course, there is no reason to anticipate that these patients would have more complications than other lung transplant recipients. Furthermore, the PH in these patients is most consistent with pulmonary arterial hypertension, raising the question of whether this should be reclassified as WHO Group 1 rather than Group 5 PH.

Declarations of interest

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Consent for publication

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Authors contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100893.

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