Case Report

Improvement of native pulmonary alveolar proteinosis after contralateral single living-donor lobar lung transplantation: A case report

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Contributions

None of the authors have conflicts of interest with commercial companies concerning this work. Conception and design: K.K., S.O.; data collection and manuscript drafting for important intellectual content: K.K., S.O., Y.S., M.E., K.N., R.S., M.A., T.S., H.O., T.W., H.K., Y.O

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Key Words

secondary pulmonary alveolar proteinosis, bone marrow transplantation, lung transplantation, macrophages, one antigen mismatch, Diamond-Blackfan-Anemia

Abbreviations

PAP; Pulmonary alveolar proteinosis, sPAP; secondary PAP, AMs; alveolar macrophages, GM-CSF; granulocyte macrophage colony stimulating factor, STAT5; signal transducer and activator of transcription 5, BMT; bone marrow transplantation, DBA; Diamond-Blackfan-Anemia, GVHD; graft versus host disease, LDLLT; living-donor lobar lung transplantation, BO; bronchiolitis

obliterans, GGO; ground glass opacification, KL-6; Krebs von den Lungen-6, HLA; human leukocyte antigen, RPLS; reversible posterior leukoencephalopathy, MMF; mycophenolate mofetil, HOT; home oxygen therapy, PFTs; pulmonary function tests, CT; computed tomography, SP-A; surfactant protein A, PAS; periodic acid Schiff, HSDT; hematopoietic stem cell transplantation.

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the accumulation of surfactant materials in the alveolar spaces due to the imbalance of surfactant homeostasis (production and clearance). We herein report a case of an eight-year-old girl who developed PAP after bone marrow transplantation (BMT) from her mother for the treatment of Diamond-Blackfan-Anemia (DBA). The anemia was improved by BMT; however, respiratory dysfunction due to graft-versus-host disease gradually progressed. She eventually underwent right single living-donor lobar lung transplantation (LDLLT) from her mother when she was 14 years old. A pathological examination of the excised lung confirmed the finding of diffuse bronchiolitis obliterans and unexpectedly revealed widespread alveolar proteinosis. Interestingly, the ground glass opacification (GGO) of her native left lung on chest X-ray was improved after LDLLT. We present the very unique clinical course of this patient and discuss the mechanisms underlying the development of PAP after BMT and its improvement after LDLLT from the same donor.

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the accumulation of surfactant materials in the alveolar spaces. Regarding the pathophysiology, alveolar macrophages (AMs) lose the ability to remove excessive sediments from the alveolar spaces. PAP is commonly classified into autoimmune (aPAP), secondary (sPAP), hereditary (hPAP), congenital (cPAP) and unclassified PAP (uPAP). aPAP accounts for 90% of cases and is associated with the existence of anti-GM-CSF (granulocyte-macrophage colony stimulating factor) auto-antibody and an increased number of alveolar foamy macrophages. GM-CSF is a monomeric glycoprotein, an activator of STAT5 phosphorylation, and an inducer of macrophage maturation. sPAP, accounting for 10% of cases, is accompanied by small and immature macrophages and mainly caused by hematological diseases, such as myelodysplastic syndrome [1-4].

We herein report a case of sPAP that developed in an eight-year-old girl after allogeneic bone marrow transplantation (BMT) from her mother for the treatment of Diamond-Blackfan-Anemia (DBA), a disease of congenital erythroblast deficiency. Although her anemia and hemosiderosis were improved by BMT, respiratory dysfunction due to graft-versus-host disease (GVHD) gradually

progressed. She eventually received right single lung lobar lung transplantation (LDLLT) from her mother when she was 14 years old. Unexpectedly, a pathological examination revealed widespread sPAP coexisting with diffuse bronchiolitis obliterans (BO), a typical pathological form of GVHD. Interestingly, the ground glass opacification (GGO) of her native left lung on chest X-ray consistent with PAP was improved after LDLLT. The levels of KL-6, which reflects the severity of PAP, were also decreased dramatically. We describe the clinical course and discuss the pathophysiological mechanisms underlying the development and remission of PAP in this case.

Case Presentation

A four-month-old girl was admitted to our hospital for the treatment of advanced anemia. As she met the diagnostic criteria of <1 year old, macrocytic anemia with no other significant cytopenia and normal marrow cellularity with a paucity of erythroid precursors, the anemia was diagnosed as DBA, a congenital erythroblast deficiency. Her familial history did not suggest any congenital diseases, including hematological disorders. Her anemia was steroid-resistant and rapidly progressive, so she was treated with frequent red blood cell transfusion. As a result, she developed hemosiderosis in her organs. Therefore, the patient received BMT at eight years old from her mother, whose HLA showed five matched haplotypes and one mismatched haplotype from the recipient.

After BMT, her anemia and hemosiderosis were improved. However, three months after the BMT, she showed symptoms of cough and dyspnea, and steroid pulse therapy and augmentation of immunosuppressive therapy were administered under the diagnosis of progressive GVHD. Cyclosporine and tacrolimus could not be used because of the occurrence of convulsion induced by reversible posterior leukoencephalopathy (RPLS) [5]. She was finally treated with prednisolone (10 mg) and mycophenolate mofetil (MMF [1500 mg]). Despite

these therapies, the severity of her dyspnea gradually progressed, and home oxygen therapy (HOT) was ultimately needed at 10 years old. Her pulmonary function tests (PFTs) immediately before lung transplantation showed severe mixed restrictive and obstructive impairments (Table 1). She was registered to the lung transplant waiting list at 12 years old. At that time, her height and weight were 120 cm and 23.3 kg, respectively.

Chest computed tomography (CT) showed diffuse cystic dilation of peripheral bronchi and widespread patchy GGO in the bilateral lung fields. While on the waiting list, her respiratory dysfunction rapidly worsened, and she eventually underwent right single LDLLT from her mother at 14 years old. The mother's right lower lobe was transplanted into the patient’s right thoracic cavity.

The pathological analysis of the excised right lung showed epithelial injury and obstruction of bronchioles with subepithelial fibrotic lesions, which was consistent with BO (Figure 1A, B). Diffuse BO was observed in the excised right lung. In addition, the retention of eosinophilic materials was observed in most alveolar spaces in all fields of the excised right lung. The alveolar eosinophilic material was positive for surfactant protein A (SP-A) and periodic acid Schiff (PAS) staining, so the diagnosis of PAP was established (Figure 1C, D). She was

negative for serum GM-CSF antibody.

She was discharged from the intensive-care unit and the hospital on days 49 and 65, respectively. She was treated with an unusual post-lung transplant immunosuppressive regimen of only 2 mg of prednisolone and 250 mg of MMF because the BMT and lung transplant donors were the same person, and the HLA of her bone marrow and the right transplanted lower lobe was identical. The courses of her postoperative imaging findings and laboratory data are shown in Figure 2. Interestingly, the GGOs that were observed in all CT sections of the left native lung gradually improved and eventually almost completely disappeared (Figure 2A). The value of KL-6, a marker reflecting the severity of the PAP [2], normalized (Figure 2B). Her hypoxia and the combined impairments with restrictive and obstructive disturbances in the PFTs were also slightly improved after lung transplantation (Figure 2B and Table 1). She remains alive and works successfully seven years after LDLLT.

Discussion

The important problem in the present case is whether we could diagnose sPAP before lung transplantation. Generally, typical PAP is associated with restrictive impairments, while BO is associated with obstructive impairments in PFTs. However, both impairments were mixed in this case. In addition, the radiographic findings were atypical of PAP or BO. Surgical lung biopsy before lung transplantation was difficult due to the invasiveness of the procedure. Thus, it might have been difficult to suspect sPAP before lung transplantation in this case. Whether or not the choice of lung transplantation using the one antigen mismatched maternal lung could be acceptable for rescuing the patient in the present case might be difficult to determine because of the lack of effective treatment for the devastating situation.

Ishii reported that sPAP patients accounted for 10% of the 404 total PAP patients (n=40) registered from 1999 to 2009 in the database of Niigata University in Japan. Blood diseases are found in 88% of sPAP patients as causal diseases, with the remaining 12% related to inflammatory and autoimmune diseases. No case associated with BMT has been reported in the database [1]. However, a careful search of the literature revealed a few reports of PAP after hematopoietic

stem cell transplantation (HSCT) and BMT [6-8]. These cases were rapidly progressive with a fatal outcome, so some cases were diagnosed by an autopsy. The authors of those reports considered that immunosuppression before and after HSCT or BMT likely suppressed the function of AMs and played a role in the development of PAP. Indeed, a retrospective study demonstrated that the use of corticosteroids induced macrophage dysfunction, which caused aPAP [9].

In the present case, PAP developed after BMT, and the patient was treated with prednisolone and MMF in an attempt to manage her GVHD. After LDLLT, the immunosuppression was weakened because the HLA of the bone marrow and the lung graft was identical (mother's marrow and lung). Therefore, the development of PAP and its remission may be attributed to the context of changes in the strength of immunosuppression, as has been described in previous reports. A pathological examination of the excised right lung showed the existence of widespread PAP and diffuse BO. These findings suggest that the improvement of GGO on CT mainly depended on the improvement of PAP, due to the diminished extent of immunosuppressive therapy after lung transplantation. Reconstruction of the lymphatic vessels was not performed in the present case; thus, the drainage of alveolar sediments from alveolar spaces via lymphatic

vessels by mechanical ventilation might be not the principal reason of improvement of GGO.

Another potential explanation for the observations made in the present study is slightly complicated. Recently, the existence of two types of AMs in the lung has been reported. One type is derived from progenitors in the fetal lung, while the other is derived from circulating monocytes differentiated from hematopoietic stem cells in bone marrow [10, 11]. Some clinicians have observed the coexistence and slow replacement of donor AMs with recipient AMs in the lung over several years in leukemia patients after BMT [12, 13]. Following BMT, the immunocompetent cells derived from the donor bone marrow may attack recipient resident AMs, thereby inducing the loss of the function of recipient AMs, which causes sPAP. The improvement in PAP after LDLLT in the present case may be explained by the hypothesis that the donor AMs from the right transplanted lung may hematogenously or lymphogenously or trans-tracheal infiltrate the left native lung, thereby weakening the attack of donor immunocompetent cells against recipient AMs or inducing chimerism of AMs with dominant donor cells. However, no conclusive studies or case reports support this hypothesis.

Despite difficulty in clearly defining the underlying mechanisms, the present case

report describes the unique clinical course of a patient with PAP who underwent BMT followed by LDLLT.

Figure legends

Figure 1. Pathology of the excised left lung. Epithelial injury and obstruction of bronchioles with subepithelial fibrotic lesions, which was consistent with bronchioliits obliterans (A: hematoxylin-eosin at 100x magnification, B: Elastica-Masson at 100x magnification). Massive eosinophilic material deposition in the alveolar space (C, hematoxylin-eosin at 100x magnification). The material in the alveolar space was positive on periodic acid-Schiff (PAS) stain (D).

Figure 2. The courses of her postoperative imaging findings and laboratory data. The ground glass opacification of the left native lung on chest X-ray and CT, which is consistent with pulmonary alveolar proteinosis, improved and eventually disappeared after right single lung lobar lung transplantation (LDLLT) (A). The value of KL-6, a marker reflecting the disease severity, normalized after LDLLT (B).

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Table 1. Pulmonary function test

	Right before lung transplantation	Half year after transplantation	Six Year after lung transplantation
VC (L)	0.59	0.85	0.84
%VC	43.4	61.6	35.6
FVC (L)	0.52	0.86	0.83
%FVC	36.9	59.7	35.2
FEV1.0 (L)	0.3	0.62	0.55
FEV1.0/FVC (%)	57.69	72.09	66.27
PEF (L)	0.72	1.53	1.2
V75 (L/S)	0.52	1.3	1.03
V50 (L/S)	0.14	0.52	0.33
V25 (L/S)	0.08	0.19	0.13
MMF (L/S)	0.14	0.36	0.27
FRC (L)			1.1
RV (L)			0.91
TLC (L)			1.75
RV/TLC (%)			52
BW (kg)	23.3	20	25
Height (cm)	120	121	120
Body surface area (m^2)	0.881	0.83	0.908

Figure 1

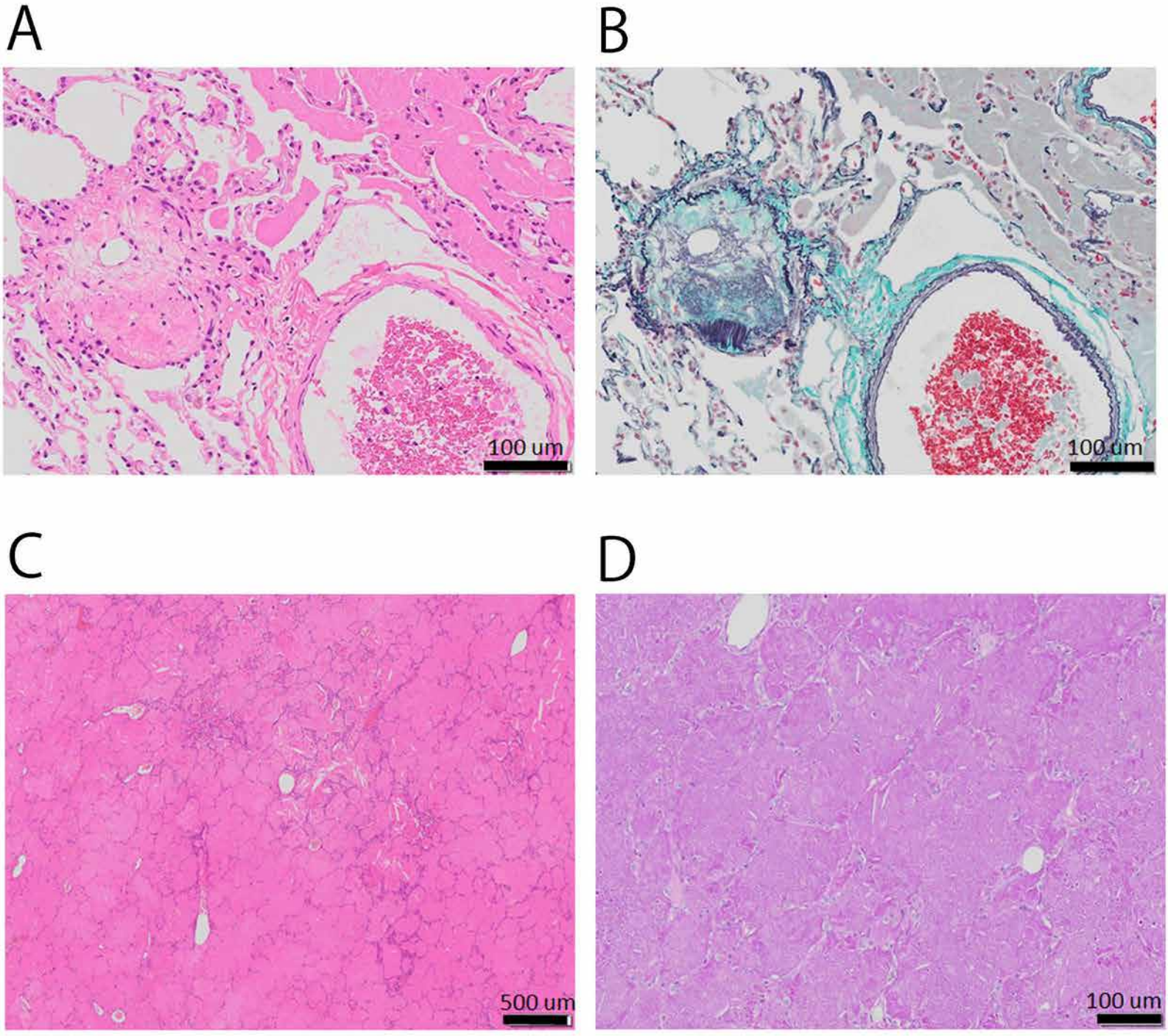
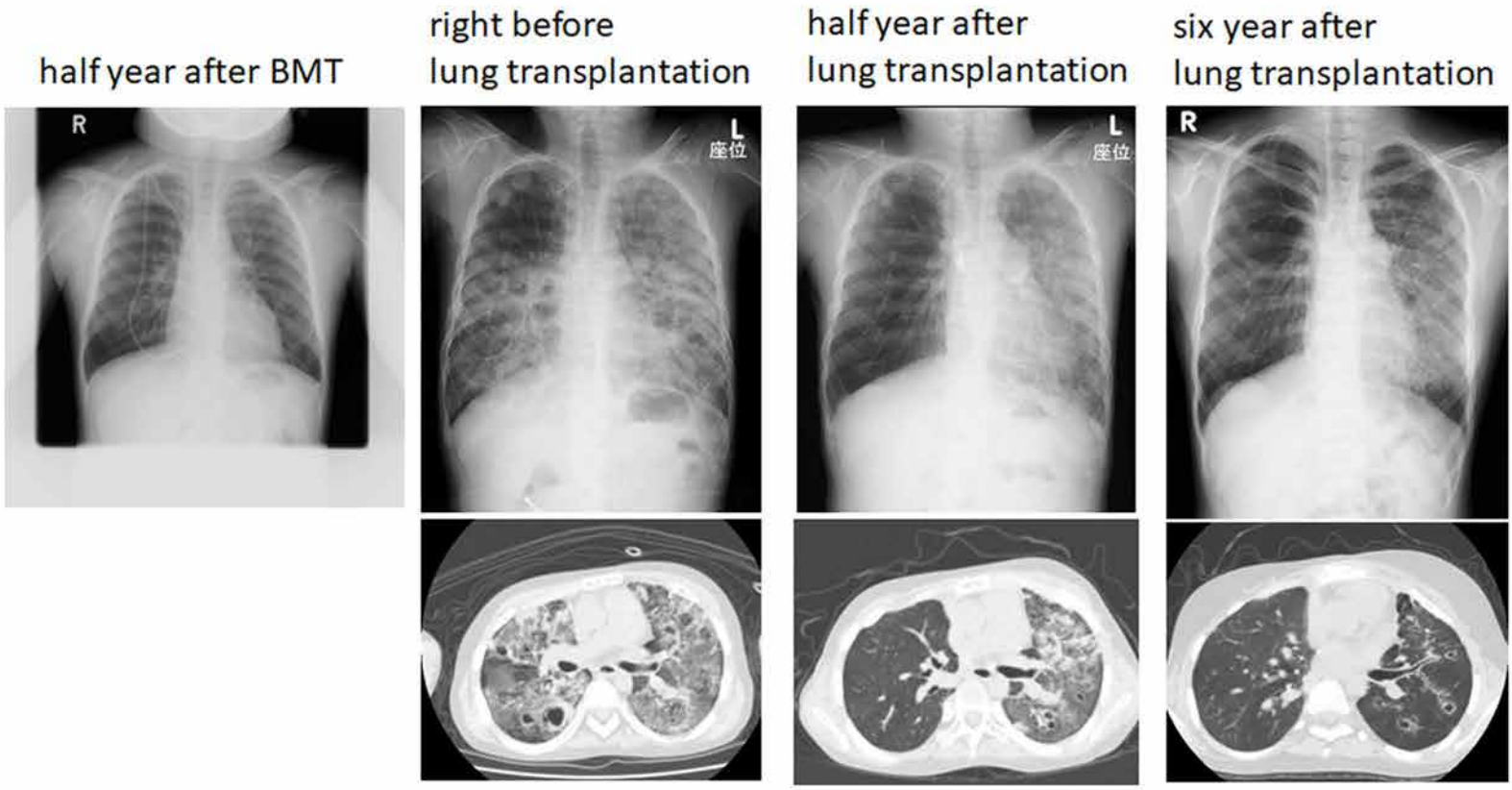
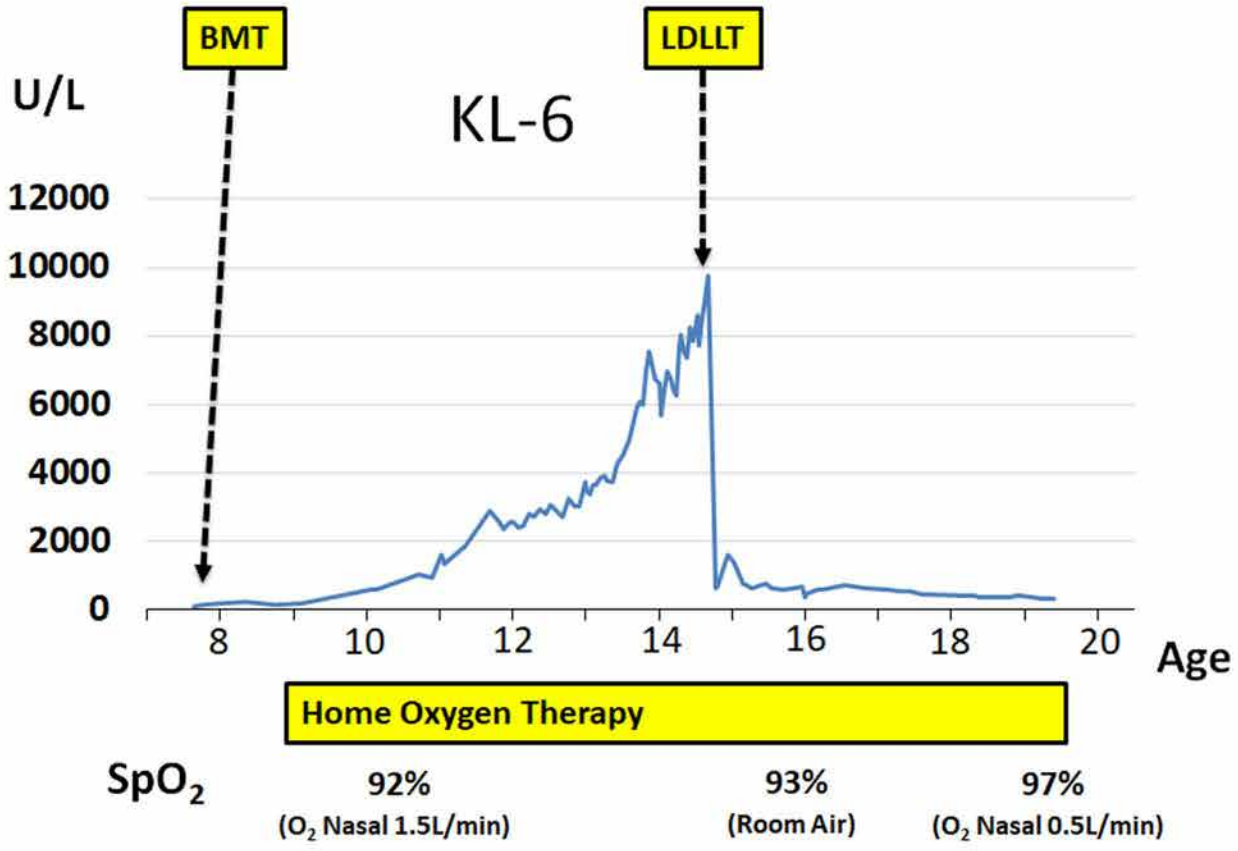


Figure 2

A


half year after BMT
right before lung transplantation
half year after lung transplantation
six year after lung transplantation
R
L
座位
L
座位
R

B


BMT
LDLLT
U/L
KL-6
12000
10000
8000
6000
4000
2000
0
8
10
12
14
16
18
20
Age
Home Oxygen Therapy
SpO2
92%
(O2 Nasal 1.5L/min)
93%
(Room Air)
97%
(O2 Nasal 0.5L/min)