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【 CASE REPORT 】

Twenty-year Follow-up of the First Bilateral Living-donor Lobar Lung Transplantation in Japan

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Abstract:

Patients with end-stage lung disease can undergo living-donor lobar lung transplantation (LDLLT), with survival rates improving every year. We herein report the 20-year follow-up findings of the first patient who underwent LDLLT in Japan. A 24-year-old woman with primary ciliary dyskinesia became ventilator-dependent after severe respiratory failure and right-sided heart failure following repeated respiratory infections. In 1998, she underwent LDLLT and received her sister's right lower lobe and her mother's left lower lobe. Although the patient required 21 hospitalizations and developed unilateral bronchiolitis obliterans syndrome, she is in good physical condition and lives without restriction at 20 years after undergoing LDLLT.

Key words: living-donor lobar lung transplantation, primary ciliary dyskinesia, cadaveric lung transplantation, long-term outcomes

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Introduction

The management of patients who have undergone lung transplantation has become increasingly important for long-term survival. In Japan, 596 lung transplants had been performed by the end of 2017. Among these, 208 were living-donor lobar lung transplantations (LDLLTs). The 5- and 10-year survival rates for LDLLT are 73.4% and 64.1%, respectively, which are similar to those for cadaveric lung transplantation (CLT) and better than international reports for LDLLT (1, 2). Twenty years have passed since the first LDLLT in Japan. We herein report the 20-year follow-up findings of the first patient to undergo LDLLT in Japan.

Case Report

In September 1998, a 24-year old woman became ventilator-dependent due to severe respiratory failure and right-sided heart failure. Chest X-rays showed bilateral opacity, and chest computed tomography (CT) showed marked bronchiectasis and consolidation (Fig. 1). The patient had been diagnosed with primary ciliary dyskinesia (PCD) at 12 years of age and regularly experienced respiratory infections and hemoptysis.

In October 1998, the patient underwent LDLLT with her sister's right lower lobe for her right side and her mother's left lower lobe for her left side under cardiopulmonary bypass at Okayama University Hospital (3, 4). A short episode of lung edema requiring nitric oxide occurred, but the procedure was uneventful. She was treated with triple immunosuppression therapy, consisting of cyclosporine A, azathioprine and corticosteroids. Two episodes of acute rejection, requiring high-dose methylprednisolone, subsequently occurred. However, the patient was discharged 61 days after LDLLT, without the need for supplementary oxygen. At dis-

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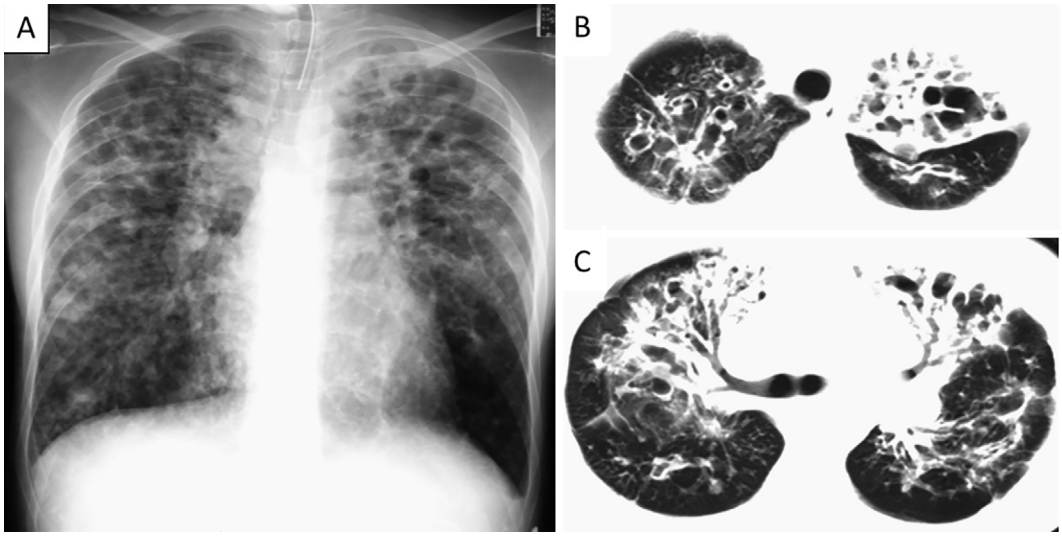

Figure 1. Preoperative chest radiography (A) showed bilateral opacity and chest computed tomography (B, C) revealed severe saccular bronchiectasis.

charge, a sputum culture indicated the presence of mucoid *Pseudomonas aeruginosa*. Nonetheless, aside from two hospitalizations due to respiratory infections in the first year following surgery, the patient was able to live without restrictions.

Preoperatively (July 1998), the patient's pulmonary function test indicated a forced expiratory volume in 1 second (FEV_1) of 0.48 L. Her postoperative FEV_1 was 1.66 L at 6 months, and it gradually increased to 2.05 L a year after LDLLT. The 6-minute walk distance at 1 year was 540 m (5). The patient's clinical course was good despite some episodes of respiratory infection requiring hospitalization, and she started a part-time job two years after LDLLT. Her FEV_1 increased to 2.25 L three years after treatment, but it began to decline thereafter.

The decline in FEV_1 three years after LDLLT indicated bronchiolitis obliterans syndrome (BOS) (6). Despite a lack of histological evidence, the patient initiated treatment for BOS because of dyspnea on exertion. The patient's immunosuppressive agents were changed from azathioprine to mycophenolate mofetil and cyclosporine A to tacrolimus. Despite this treatment, the patient's FEV_1 further decreased to 1.43 L in the four years after LDLLT. Therefore, the patient was administered high-dose methylprednisolone and OKT-3, an anti-CD3 monoclonal antibody. Subsequently, BOS appeared only in the left lung, as observed with ventilation/perfusion scintigraphy, and the decline in FEV_1 stopped between 1.10 and 1.20 L (Fig. 2). Because the blood level of tacrolimus was difficult to adjust in this patient, it was replaced with cyclosporine A. Although the patient was admitted once a year due to respiratory infection, she was essentially able to continue living and working without restrictions excluding strenuous exercise.

In February, 19 years after LDLLT, the patient was admitted to hospital with dyspnea and fever, and she was diagnosed as having bacterial pneumonia. She was treated with intravenous antibiotics (meropenem and azithromycin). Five days after admission, the patient had hemosputum, and chest CT indicated the expansion of consolidation and traction bronchiectasis in the right lung (Fig. 3). We performed bronchoalveolar lavage for the differential diagnosis and found a 33.1% increase in the number of lymphocytes and a negative bacterial culture. Considering the risks, we did not conduct transbronchial lung biopsy. Organizing pneumonia associated with bacterial pneumonia or late-onset acute lung rejection was considered. The patient was treated with intravenous high-dose methylprednisolone and intravenous immunoglobulin (IV-Ig) therapy, and her condition subsequently improved. Furthermore, a donor-specific antibody test was negative. Thus, we considered the patient to be negative for acute lung rejection and instead diagnosed her with organizing pneumonia associated with bacterial pneumonia.

Twenty years after LDLLT, chest CT revealed an improvement in consolidation (Fig. 4). At this time, the patient's FEV_1 was 1.13 L and her 6-minute walk distance was 530 m. In the past 20 years, the patient had required 21 hospitalizations (for 16 airway infections, 1 shingles, 1 gastroenteritis, 1 dental infection, and 2 treatment change). However, she has been living without restrictions for 20 years after LDLLT.

Discussion

In this case report, we describe the progress of the first patient to receive LDLLT in Japan after 20 years. In general, the patient is in good physical condition and has been living without restrictions following treatment.

LDLLT was developed in the USA for patients with severe lung disease who would not survive the long waiting period for CLT (7). The number of CLTs has increased since 2010, when the Japanese Organ Transplant Law was

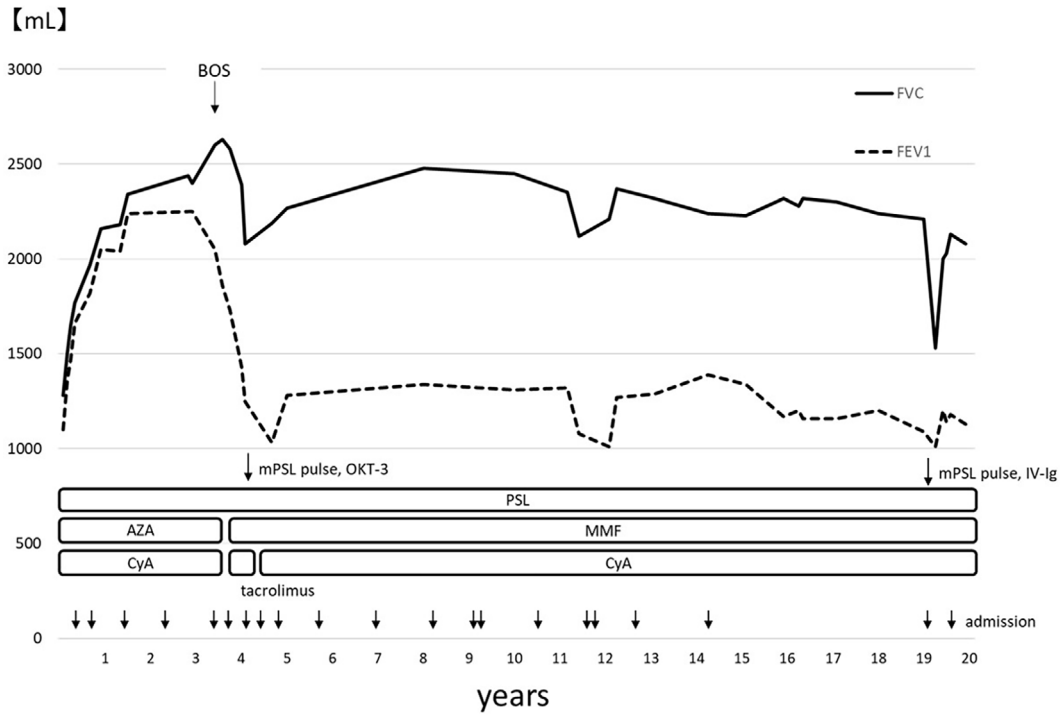

Figure 2. **Progression of the patient's forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) after living-donor lobar lung transplantation. AZA: azathioprine, BOS: bronchiolitis obliterans syndrome, CyA: cyclosporine A, MMF: mycophenolate mofetil, mPSL: methylprednisolone**

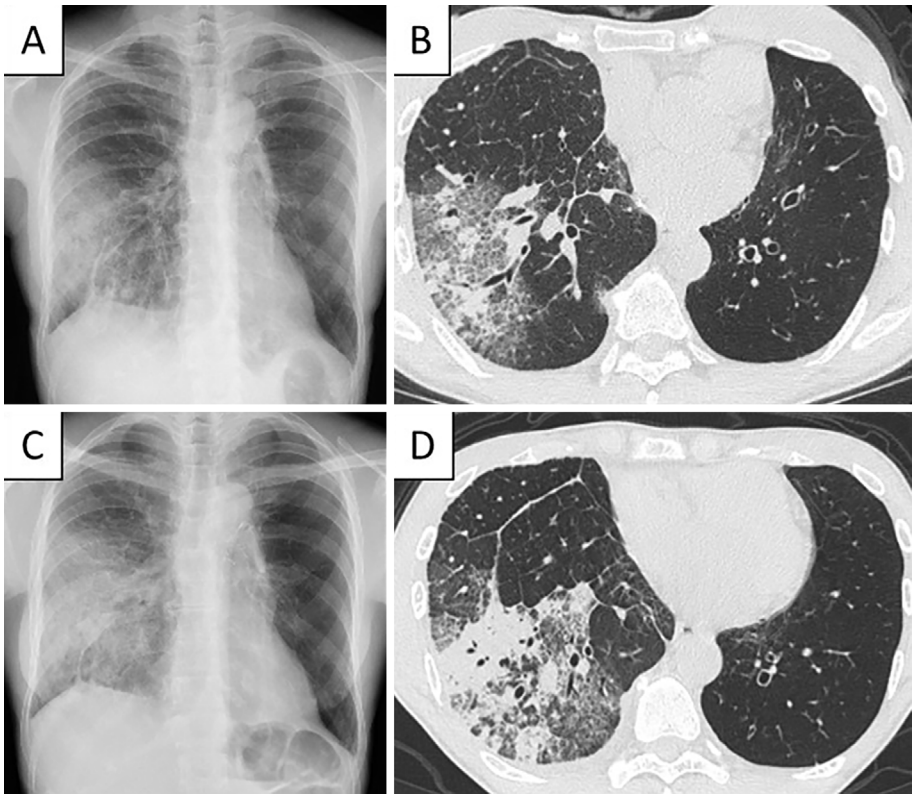

Figure 3. **Chest radiography (A) and chest computed tomography (CT) (B) in February 19 years after living-donor lobar lung transplantation, demonstrating consolidation in the right lung. Chest radiography (C) and CT (D) 5 days after admission revealed an expansion of consolidation and traction bronchiectasis despite treatment with antibiotics.**

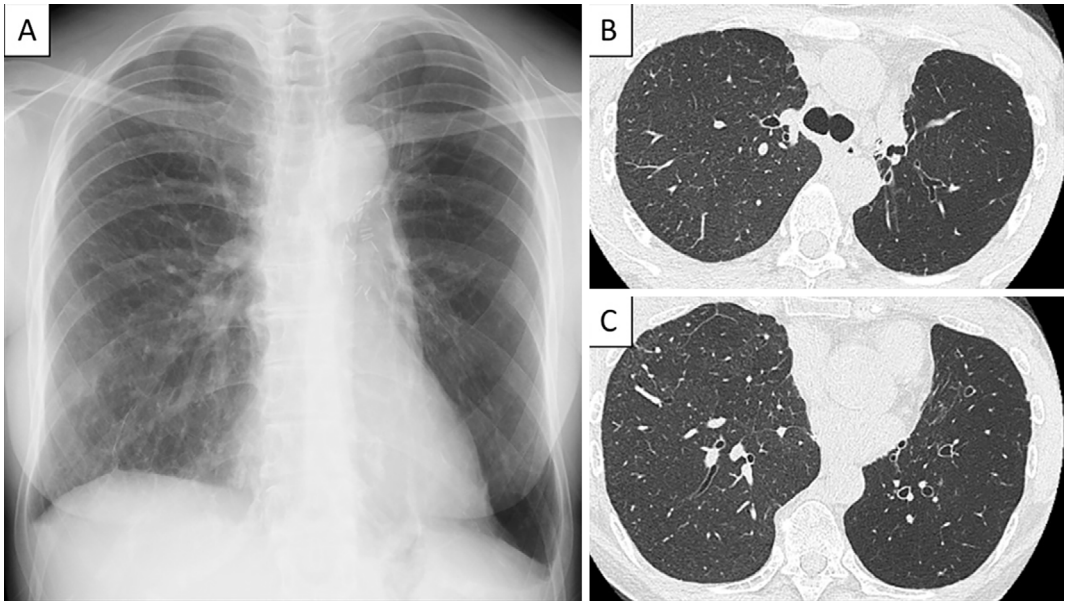

Figure 4. **Chest radiography (A) and chest computed tomography (B, C) 20 years after living-donor lobar lung transplantation, showing an improvement of consolidation.**

amended. Nonetheless, LDLLT remains an option if donor lungs are available because of the long waiting period (exceeding 800 days) and the high mortality rate of those on the waiting list for CLT.

In Japan, 208 LDLLTs had been performed by the end of 2017. The 5- and 10-year survival rates for LDLLT in Japan are 73.4%, and 64.1%, respectively (1). These are similar to those for CLT in this country. In contrast, according to international registry reports, the 5- and 10-year survival rates for adult lung transplant from January 1990 to June 2016 were 55% and 33%, respectively (8).

Currently, only 10 institutions perform lung transplantation in Japan. Undoubtedly, their expertise and strict perioperative and postoperative management of lung transplantation lead to good results. Most patients living in cities visit local hospitals for regular follow-up after the acute phase of lung transplantation. The survival rates for lung transplantation are improving every year (2), and the number of patients who undergo lung transplantation is also increasing. Therefore, thoracic physicians working in local hospitals should ensure that they are familiar with the management of lung transplantation patients.

PCD is a rare lung disease characterized by impaired mucociliary clearance. Patients with PCD accompanied by situs inversus and chronic sinusitis are diagnosed with Kartagener syndrome. Hayes et al. (9) reported the outcomes of lung transplantation for PCD and Kartagener syndrome, suggesting no difference in the overall survival in patients with PCD undergoing lung transplantation compared with the survival rates in those with idiopathic pulmonary fibrosis, cystic fibrosis, and chronic obstructive pulmonary disease who undergo lung transplantation.

There are some advantages of LDLLT over CLT. For example, LDLLT has a shorter duration of ischemia than CLT (10), which appears to contribute to a lower frequency of primary graft failure and airway complications after lung transplantation (11). Chronic lung allograft dysfunction, including BOS, is the major cause of death in CLT patients. In many cases of LDLLT, recipients develop unilateral BOS. However, in bilateral LDLLT, the recipient receives two lobes from different donors which may provide a long-term benefit because the contralateral unaffected lung may function as a reservoir in case of unilateral BOS (12). Indeed, in this case, the patient had unilateral BOS and a decline in FEV_1.

In this patient, OKT-3, an anti-CD3 monoclonal antibody was used to treat BOS. At that time, OKT-3 was used in lung transplantation, but it is no longer used today (13). No optimal treatment for BOS has yet been established, although it is suggested that it may be beneficial to prescribe azithromycin or to switch the immunosuppressive agent (conversion of cyclosporine A to tacrolimus) (14).

Long-term care after LDLLT is also important. The most common causes of late death in such lung transplantation patients have been reported to be chronic lung allograft dysfunction, infection, and malignancy such as post-transplant lymphoproliferative disease (2). In contrast, the rate of death from late-onset acute lung rejection after lung transplantation is only 2.4% (2). We previously reported a case of late-onset acute lung rejection that may have been activated by pneumonia, in which the patient died 11 years after LDLLT (15). Therefore, we should pay close attention to the possibility of acute lung rejection after respiratory infection because a high incidence of acute lung rejection is observed in lung transplantation patients following community-acquired respiratory infections (16).

Indeed, the episode of pneumonia 19 years after LDLLT in this case was a matter of concern due to the possibility of

acute lung rejection. Hence, we provided treatment with high-dose methylprednisolone and IV-Ig. The presence of donor-specific antibody has been reported to be associated with acute rejection (17). Although we can only speculate because we could not evaluate any lung tissue specimens, we consider this episode to be organizing pneumonia associated with bacterial pneumonia based on the results of therapeutic response and a negative result for donor-specific antibody.

In conclusion, we described the long-term successful outcome after 20 years in the first patient who underwent LDLLT in Japan. CLT has increased since changes to Japanese transplantation laws in 2010, but LDLLT remains an important option for patients with end-stage lung diseases. Our findings indicate that long-term care is extremely important for lung transplant recipients.

Informed consent for the publication of these clinical details was obtained from the patient and her family.

The authors state that they have no Conflict of Interest (COI).

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