Lung transplantation for diffuse panbronchiolitis: 5 cases from a single centre†

Seiichiro Sugimotoa,*, Kentaroh Miyoshia, Masaomi Yamanea and Takahiro Otob

Abstract

Diffuse panbronchiolitis is a rare complex genetic disease predominantly affecting East Asians, and is characterized by chronic inflammation of the respiratory bronchioles and sinobronchial infection. Although long-term macrolide therapy has been shown to significantly improve the survival in patients with diffuse panbronchiolitis, some patients continue to deteriorate, eventually requiring lung transplantation. However, lung transplantation for diffuse panbronchiolitis has rarely been reported and the outcome in these patients remains unknown. We describe our experience of lung transplantation for diffuse panbronchiolitis. A total of 5 patients received long-term macrolide therapy and had airway colonization by Pseudomonas aeruginosa preoperatively. Three patients had undergone sinus surgery for chronic rhinosinusitis before the transplantation. Bilateral cadaveric lung transplantation was performed in 4 patients, and living-donor lung transplantation in 1. After the lung transplantation, 1 patient developed an A3 acute rejection episode; however, none of the recipients developed severe pneumonia or any fatal infections. One recipient developed chronic lung allograft dysfunction 3 years after the transplantation; however, none developed recurrence of diffuse panbronchiolitis. All of the 5 patients were still surviving after a median follow-up period of 4.9 years (3.7–12.3 years). Lung transplantation is a viable option for the treatment of progressive diffuse panbronchiolitis resistant to long-term macrolide therapy.

Keywords: Lung transplantation • Lung infection • Recurrence • Bronchiolitis obliterans • Rejection • Outcomes

INTRODUCTION

Diffuse panbronchiolitis (DPB) is a rare complex genetic disease predominantly affecting East Asians [1, 2]. In addition to the limited number of DPB cases reported from outside East Asia, about a half of the limited number of DPB cases reported from Western countries are Asian immigrants [2]. While DPB is frequently compared with cystic fibrosis, a common genetic disease encountered in Caucasians, neither pancreatic insufficiency nor any obvious abnormalities of the sweat electrolytes are seen in DPB, and the two are considered to be entirely different diseases [2]. Clinically, DPB is characterized by chronic inflammation of the respiratory bronchioles and sinobronchial infection [1, 2]. Moreover, DPB is a progressive suppurative and obstructive airway disease, resulting in bronchiectasis, respiratory failure and death, if left untreated [2]. Long-term therapy with macrolide antibiotics has been shown to significantly improve the survival of DPB patients [1]; however, some DPB patients deteriorate despite macrolide therapy, eventually requiring lung transplantation (LTx). To date, LTx for progressive DPB patients has rarely been reported, except for a case of early recurrence of DPB after LTx [3] and our successful case [4], and the outcomes of LTx for progressive DPB are unknown. In this study, we describe our experience of LTx for DPB.

CLINICAL SUMMARY

Between October 1998 and March 2014, we performed 124 LTx, including 51 cadaveric LTx and 73 living-donor lobar LTx in patients with various end-stage lung diseases. Among these, 5 patients were cases of DPB. The patients’ characteristics are reported in Table 1 [4]. After the clinical diagnosis of DPB (Fig. 1), all 5 patients received long-term macrolide therapy for 5–20 years. Pseudomonas aeruginosa was preoperatively isolated in the sputum of all 5 patients. According to the results of otolaryngological examination, 3 of the 5 patients had undergone sinus surgery for severe rhinosinusitis before the LTx, while the remaining 2 patients had received only nasal care. Non-invasive positive pressure ventilation had been adopted in 2 of the 5 patients before the LTx. One patient had had a brain abscess that had been treated before he was registered on the LTx waiting list, whereas another patient had secondary pulmonary
hypertension associated with progressive DPB. The median waiting time for the LTx was 709 (371–1029 days).

Four patients underwent bilateral cadaveric LTx, whereas the remaining 1 patient underwent bilateral living-donor lobar LTx. Cardiopulmonary bypass was used in all the 5 patients during the LTx. The median ischaemic time of the second graft was 463 (160–787 min). One patient with grade 3 primary graft dysfunction required postoperative extracorporeal membrane oxygenation. In all the 5 recipients, the post-transplant immunosuppression therapy consisted of tacrolimus, mycophenolate mofetil and corticosteroid. One recipient developed steroid-resistant acute A3 rejection diagnosed by open lung biopsy, which necessitated OKT3 administration.

In the postoperative period, the only recipient of living-donor lobar LTx developed pneumothorax, which necessitated a repair operation. Another recipient was diagnosed as having rectal cancer 14 months after the LTx, which necessitated colorectal resection. None of the recipients developed severe pneumonia or fatal infectious diseases. Pseudomonas aeruginosa, which was detected in the sputum of all the recipients before the LTx, disappeared temporarily from the sputum within 1 year after the LTx. Four of the 5 patients, including 2 patients who had not undergone sinus surgery, developed pseudomonal airway recolonization in the long term after LTx. Histological examination revealed chronic inflammation localized mainly in the respiratory bronchioles with characteristic interstitial accumulation of foamy histiocytes and lymphocyte infiltration, suggestive of diffuse panbronchiolitis (haematoxylin and eosin staining ×40).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Age/sex</td>
<td></td>
<td>37/F</td>
<td>27/M</td>
<td>36/F</td>
<td>40/F</td>
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<td>7</td>
<td>9</td>
<td>6</td>
<td>20</td>
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<tr>
<td>Pseudomonal colonization</td>
<td></td>
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<td>Yes</td>
<td>Yes</td>
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<td></td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>NIPPV</td>
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<td>Comorbidity</td>
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<td>Brain abscess</td>
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<td>None</td>
<td>Secondary PH</td>
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<tr>
<td>Waiting time (days)</td>
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<td>874</td>
<td>544</td>
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<tr>
<td>Lung transplant donor</td>
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<td>Living</td>
<td>Brain-dead</td>
<td>Brain-dead</td>
<td>Brain-dead</td>
<td>Brain-dead</td>
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<tr>
<td>Total number of HLA-A, HLA-B and HLA-DR mismatches</td>
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<td>6</td>
<td>2</td>
<td>5</td>
<td>4</td>
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<td>Graft ischaemic time (min)</td>
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<td>578</td>
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<td>Acute rejection episode (frequency)</td>
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<td>Post-transplant complication</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>Rectal cancer</td>
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<td>CLAD</td>
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<td>Follow-up period (years)</td>
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<td>5.1</td>
<td>4.9</td>
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<td>3.7</td>
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</tbody>
</table>

CLAD: chronic lung allograft dysfunction; DPB: diffuse panbronchiolitis; HLA: human leucocyte antigen; NIPPV: non-invasive positive pressure ventilation; PGD: primary graft dysfunction; PH: pulmonary hypertension.
**DISCUSSION**

Because LTx is not yet commonly practised in East Asia, which is the region most individuals with DPB reside in, the outcomes of LTx for DPB have never been reported. To the best of our knowledge, this is the first report of long-term outcomes of LTx for DPB. In this study, no cases of recurrence of DPB were encountered in the long term after LTx. Recurrence of DPB 10 weeks after LTx was reported two decades ago, which was the first report of recurrence of the native lung disease after LTx [3]. Subsequently, recurrence developing 4 months after LTx was reported in 2 cases of diffuse bronchiectasis [5], which had been preoperatively diagnosed as DPB. In these cases, sinus surgery or nasal care for chronic rhinosinusitis seemed not to have been performed before the LTx [5]. In this study, control of rhinosinusitis with sinus surgery or chronic nasal care might be important in preventing recurrence of DPB and fatal infection after LTx. However, 1 patient receiving only nasal care developed CLAD after the LTx. Pretransplant sinus surgery might be required to prevent the development of CLAD in DPB patients, similar to patients with cystic fibrosis.

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Conflict of interest: none declared.

**REFERENCES**


**eComment.** Benefits of macrolide usage and bacteriological profile in patients with diffuse panbronchiolitis

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We read with great interest the article by Sugimoto et al. [1] where they described their experience with lung transplantation for diffuse panbronchiolitis (DPB), a chronic, idiopathic airways disease primarily affecting the East Asian population. Our aim is to appraise certain authors’ statements by using the current evidence on the benefits of macrolide usage in patients with DPB, as well as to assess the bacteriological profile in those with this long-term condition.

Despite the need for lung transplantation in certain progressive DPB patients (as described in this paper), it is well known that the advent of macrolide therapy has substantially changed the disease prognosis due to its anti-inflammatory and immunoregulatory effects. Hence the statement by the authors that the long-term macrolide therapy has been shown to significantly improve the survival in patients with DPB can be considered legitimate.

Still, a Cochrane review on this topic has emphasized the absence of high-quality evidence to support the usage of macrolides in the treatment of DPB, as the use of macrolides for this indication is based on retrospective and non-randomized controlled studies [2]. Even so, the Cochrane review states that, for the time-being, the use low-dose macrolides soon after establishing a diagnosis is a reasonable approach, extending their use for at least six months (in accordance to current guidelines) [2].

The Cochrane review also cautions that additional insights are definitely required on the subset of patients more likely to benefit from this treatment approach, as well as more information on the most suitable dose, type and duration of administration [2]. Since some patients in this study by Sugimoto et al. received macrolide therapy for up to 20 years and still deteriorated [1], proper assessment of the treatment efficacy and rationale for continuing macrolide therapy over protracted time periods in non-responsive patients should be addressed earlier in the course of disease.

The authors further state that *Pseudomonas aeruginosa (P. aeruginosa)* was preoperatively isolated in the sputa of all five patients, which is an expected finding in the late course of the disease, as detection rates of *P. aeruginosa* rise to 60% or more after four years of treatment [3]. Nonetheless, no information was given as to whether the samples were tested for some other pathogens, which could also have been found in the sputa of patients with DPB, such as *Haemophilus influenzae* [3,4].

More importantly, defects of mucociliary clearance found in DPB may predispose individuals to infection with non-tuberculous mycobacteria (NTM) [5].

In a recent retrospective study from Japan, Tsuji et al. found that the overall prevalence of NTM in DPB was 21.2%, which was higher than the previous surveillance of NTM in the general Japanese population [5]. The most common isolate was *Mycobacterium avium* complex followed by *Mycobacterium kansasii* and *Mycobacterium chelonae* [5]. Such high prevalence of NTM associated with DPB raises concerns of generating macrolide-resistant NTM infections due to the use of clarithromycin in monotherapy of patients with DPB. Therefore, the presence of these mycobacteria should be confirmed or excluded by appropriate microbiological analysis.

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References


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