Unilateral chronic lung allograft dysfunction is a characteristic of bilateral living-donor lobar lung transplantation

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Abstract

OBJECTIVES: Living-donor lobar lung transplantation (LDLLT) has been established as a life-saving procedure for critically ill patients who cannot wait for cadaveric lung transplantation. Chronic lung allograft dysfunction (CLAD) is the main cause of late morbidity and mortality in lung transplantation. Studies on CLAD in cadaveric lung transplantation have been extensively reported, but few reports have been reported concerning CLAD after LDLLT. The aim of this study was to determine the prevalence, characteristics and prognosis of CLAD after LDLLT.

METHODS: Among 38 patients who survived more than 3 months after LDLLT at Kyoto University Hospital between June 2008 and December 2013, 8 patients (21%) were diagnosed with CLAD. The mean follow-up period after LDLLT was 33 months. Clinical course, pulmonary function and radiological findings were reviewed retrospectively in all the 38 patients as of May 2014.

RESULTS: Six patients were female and 2 were male. The median age at LDLLT was 31 years, and the median interval between LDLLT and the initial diagnosis of CLAD was 23 months. Among 8 patients who developed CLAD, 2 patients underwent right single LDLLT and 6 patients underwent bilateral LDLLT. The former 2 patients survived 44 and 47 months after the treatment. Five out of 6 patients with bilateral LDLLT developed unilateral CLAD at the time of initial diagnosis according to ventilation scintigraphy. In 3 of these 5 patients, the progression of CLAD was halted by treatment, and the median follow-up period of 33 months after treatment. In the remaining 2 of 5 patients, CLAD progressed to the contralateral lung metachronously; 1 patient survived without oxygen supplement, but the other patient required reperformance of LDLLT 3 years after the first one. One patient with bilateral CLAD at the time of detection died of disease progression 4 years after LDLLT.

CONCLUSIONS: Despite a relatively short observation time, CLAD developed in approximately one-fifth of the patients who survived more than 3 months after LDLLT. In bilateral LDLLT, CLAD developed unilaterally in most cases, which might be beneficial in the long term because the unaffected contralateral lung may function as a reservoir.

Keywords: Chronic lung allograft dysfunction • Living-donor lobar lung transplantation • Lung transplantation

INTRODUCTION

Living-donor lobar lung transplantation (LDLLT) was first described in 1992 and since then, it has been developed as a life-saving procedure that provides similar survival as cadaveric lung transplantation [1–3]. In Japan, which still has a severe donor shortage problem [4], LDLLT is an important option for critically ill patients.

Chronic lung allograft dysfunction (CLAD), which is also referred to as chronic rejection, remains a major limitation to the long-term success of lung transplantation. Bronchiolitis obliterans syndrome (BOS) is a major type of CLAD and has been defined to allow uniformity of description and grading of severity throughout the world, therefore, many studies on BOS in cadaveric lung transplantation have been reported [5–7]. However, only a single report was done concerning CLAD after LDLLT, in which only the prevalence and laterality of CLAD after LDLLT was described [8]. The aim of this study was to determine the prevalence, characteristics and prognosis of CLAD after LDLLT.

PATIENTS AND METHODS

A review of the lung transplantation database identified 8 patients with CLAD after LDLLT at Kyoto University Hospital between June 2008 and December 2013. During this period, 42 patients underwent LDLLT with a 3-year survival rate of 86.1% and median follow-up period of 30 months. Thirty-eight patients survived...
more than 3 months after the transplantation, and 4 patients were excluded because of in-hospital death or follow-up period of less than 3 months after LDLLT (Fig. 1).

Each transplantation was basically indicated according to the inclusion criteria described elsewhere [2]. Size disparity was acceptable only when the forced vital capacity (FVC) of the donor lobe was 45% or more of the predicted FVC of the recipient (calculated according to height, age and gender). The inpatient and outpatient medical records were retrospectively reviewed for all patients. The surgical procedures of donor lobectomy and graft implantation were previously described elsewhere [2, 9, 10].

Postoperative immunosuppression consisted of triple-drug therapy with cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil and corticosteroids. In cases of acute rejection, which were judged on the basis of radiographic and clinical findings without transbronchial lung biopsy, patients were treated with a daily bolus dose of 10 mg/kg methylprednisolone for 3 days. Prophylactic administrations of antibacterial, antimitotic and antiviral agents were applied to all patients. After discharge, patients visited the outpatient clinic once every month. Further, patients underwent ventilation scintigraphy at 3, 6 and 12 months after surgery and annually from then on.

In order to monitor for new onset airflow limitation, all patients were subjected to a daily simple spirometry test to measure daily FVC and forced expiratory volume in 1 s (FEV1) at home. If the home spirometry test showed a decline in measurements, they were examined more closely by precise spirometry at the clinic. New onset of airflow limitation was monitored by establishing a baseline value, which was taken as the average of the two highest values of FEV1 obtained at least 3 weeks apart and without proceeding bronchodilator inhalation. Thus, the diagnosis of CLAD was conducted based on the guidelines of the International Society for heart and lung transplantation and the classification proposed by Estenne et al. [5], which used the severity of airflow limitation as determined by a decrease in FEV1 to reflect the presence and severity of classical BOS.

All the data were reviewed retrospectively to evaluate the prevalence, characteristics and prognosis of CLAD after LDLLT as of 31 May 2014.

RESULTS

Patients’ characteristics and the status of chronic lung allograft dysfunction

Among 38 patients who survived more than 3 months after LDLLT with the median follow-up period of 33 months, CLAD developed in 8 patients (21.1%) with a proportion of 2 males and 6 females. The age at the transplantation ranged from 6 to 52 years. The median interval between LDLLT and the diagnosis of CLAD was 23 months (range: 12–36). The median follow-up period after the initial diagnosis was 36 months (range: 7–48). Overall survival and CLAD-free survival curves are shown in Fig. 2. Three-year overall survival and CLAD-free survival rates were 85.9 and 65.2%, respectively.

Table 1 shows the patients’ characteristics and the status of CLAD at initial detection. Cases 1, 2 and 4 were paediatric patients. Single LDLLT was conducted in 2 patients and bilateral LDLLT in 6 patients. The original diseases were bronchiolitis obliterans (BOs) after haematopoietic stem cell transplantation (HSCT) in 3 patients, idiopathic interstitial pneumonia (IIP) in 2 patients, bronchiectasis in 1 patient, BO accompanying Stevens–Johnson syndrome (SJS) in 1 patient and interstitial pneumonia associated with clinically amyopathic dermatomyositis (CADM) in 1 patient. In the interval between LDLLT and the diagnosis of CLAD, cytomegalovirus infections were detected in 3 patients. Acute rejection was clinically diagnosed in 7 of 8 patients, and responded well to the corticosteroid pulse therapy. Antibody-mediated rejection was found in 1 patient (Case 3).

At the time of diagnosis, the decreasing degree of FEV1 ranged from 2.5 to 58.7% compared with the baseline. High resolution computed tomography detected hyperinflation in 1 patient, traction bronchiectasis in 1 patient, mosaic patterns in lung fields in 1 patient and increased reticular opacities in 3 patients, all of which are known as typical signs of obstructive CLAD. Ventilation scintigraphy revealed unilateral air-trapping in 5 of 6 patients with CLAD who had undergone bilateral LDLLT (Cases 3–5, 7 and 8), and bilateral air-trapping in 1 patient (Case 6). In 2 of 5 patients with
unilateral CLAD at the time of diagnosis, signs of air-trapping appeared in the contralateral lung during the follow-up period (Cases 3 and 5). Regarding 2 paediatric patients who had undergone single LDLLT, we diagnosed CLAD by comparing washout with former findings in ventilation scintigraphy. The phenotype of CLAD was classified into three groups (BOS; RAS: restrictive allograft dysfunction; ARAD: azithromycin responsive allograft dysfunction) [11].

The characteristics of donor factors
Table 2 shows the characteristics of donor factors. The number of human leucocyte antigen (HLA) typing (HLA-A, HLA-B and HLA-DR) mismatches per donor lobe ranged from 2 to 6. Preoperatively, anti-HLA antibodies were detected in 1 patient (Case 8) using the LABScreen Single Antigen assay (One Lambda, Inc., Canoga Park, CA, USA). This was donor-specific antibody with the mean fluorescence

Table 1: Patients’ characteristics and the status of CLAD

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Original disease</th>
<th>Single LDLLT or Bilateral LDLLT</th>
<th>CLAD status at initial detection</th>
<th>Months after Tx</th>
<th>Stage at detection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>Female</td>
<td>BO (SJS)</td>
<td>Single LDLLT (Rt)</td>
<td>BOS</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Female</td>
<td>BO after HSCT</td>
<td>Single LDLLT (Rt)</td>
<td>ARAD</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>Female</td>
<td>IIP</td>
<td>Bilateral LDLLT</td>
<td>BOS</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Male</td>
<td>BO after HSCT</td>
<td>Bilateral LDLLT</td>
<td>ARAD</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>Female</td>
<td>Bronchiectasis</td>
<td>Bilateral LDLLT</td>
<td>BOS</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>Male</td>
<td>BO after HSCT</td>
<td>Bilateral LDLLT</td>
<td>ARAD</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>Female</td>
<td>IIP</td>
<td>Bilateral LDLLT</td>
<td>BOS</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>Female</td>
<td>IP (CADM)</td>
<td>Bilateral LDLLT</td>
<td>BOS</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

LDLLT: living-donor lobar lung transplantation; Tx: transplantation; CLAD: chronic lung allograft dysfunction; BO: bronchiolitis obliterans; SJS: Stevens-Johnson syndrome; HSCT: haematopoietic stem cell transplantation; IIP: idiopathic interstitial pneumonia; ARAD: azithromycin responsive allograft dysfunction; IP: interstitial pneumonia; CADM: clinically amyopathic dermatomyositis.

Table 2: The characteristics of donor factors (Right/Left)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Genetic relationship</th>
<th>CMV mismatch</th>
<th>Ischaemic time (m)</th>
<th>HLA typing mismatches (n)</th>
<th>Preoperative anti-HLA antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35/-</td>
<td>F/-</td>
<td>Mother/-</td>
<td></td>
<td>95/-</td>
<td>2/-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>33/-</td>
<td>F/-</td>
<td>Mother/-</td>
<td></td>
<td>80/-</td>
<td>3/-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>33/60</td>
<td>M/F</td>
<td>Husband/Mother</td>
<td></td>
<td>172/117</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>44/42</td>
<td>M/F</td>
<td>Father/Mother</td>
<td>Right donor</td>
<td>159/107</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>24/23</td>
<td>M/F</td>
<td>Son/Daughter</td>
<td></td>
<td>204/135</td>
<td>3/3</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>50/54</td>
<td>M/F</td>
<td>Brother/Wife</td>
<td></td>
<td>193/151</td>
<td>3/6</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>58/53</td>
<td>F/F</td>
<td>Mother/Ant</td>
<td></td>
<td>189/132</td>
<td>2/5</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>20/22</td>
<td>M/F</td>
<td>Son/Daughter</td>
<td></td>
<td>196/115</td>
<td>2/2</td>
<td>DSA</td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus; HLA: human leucocyte antigen; DSA: donor-specific antibody.

Table 3: Medication against CLAD and outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Medication against CLAD</th>
<th>Outcome</th>
<th>F/u period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corticosteroid</td>
<td>AZM</td>
<td>IS switch/add-on</td>
</tr>
<tr>
<td>1</td>
<td>Pulse therapy</td>
<td>+</td>
<td>AZA -&gt; MMF</td>
</tr>
<tr>
<td>2</td>
<td>Dose up</td>
<td>+</td>
<td>AZA -&gt; MMF</td>
</tr>
<tr>
<td>3</td>
<td>Pulse therapy</td>
<td>+</td>
<td>Sustained-release tacrolimus</td>
</tr>
<tr>
<td>4</td>
<td>Pulse therapy</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Pulse therapy</td>
<td>+</td>
<td>CSA -&gt; FK</td>
</tr>
<tr>
<td>6</td>
<td>Pulse therapy</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Pulse therapy</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Pulse therapy</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
intensity (MFI; DR14 = 1633), but preoperative anti-human globulin complement-dependent cytotoxicity cross-match and flow cytometry cross-match (FCXM) methods were negative. In all patients, preoperative lymphocyte cross-matching and FCXM were negative.

Medical interventions against chronic lung allograft dysfunction and clinical courses

Table 3 summarizes the medications against CLAD and the outcome. Regarding treatments for CLAD, we conducted corticosteroid pulse therapy in 7 patients and raised corticosteroid dose temporarily in 1 patient. Long-term administration of azithromycin was initiated in all patients at the time of diagnosis. A change in immunosuppressive agents was applied to 4 patients (Cases 1-3 and 5).

The trends of FEV₁ were favourable in 1 patient with unilateral CLAD after single LDLLT and 3 patients with unilateral CLAD after bilateral LDLLT (Cases 2, 4, 7 and 8). Especially, in Case 7, the FEV₁ turned to increase a few months after introduction of azithromycin. The clinical status of this case appeared to correspond to ARAD. On the other hand, the graft functions continued to deteriorate in the other 4 patients (Cases 1, 3, 5 and 6); 2 of them finally lost the graft function. In Case 3, reperformance of LDLLT was required due to severe progression of CLAD. Immunohistochemistry of the extracted lobes revealed that intense endothelial C4d deposition was observed in peribronchial capillaries adjacent to bronchioles [12, 13]. Case 6 passed away due to loss of graft function 4 years after the transplantation.

Ventilation scintigraphy detected air-trapping at the time of diagnosis based on the decline of FEV₁ in 7 patients (Cases 1, 2 and 4-8) and prior to the diagnosis in 1 patient (Case 3). Excluding 1 patient who underwent retransplantation, there was no disappearance in air-trapping after medical interventions despite some cases with a favourable trend of FEV₁ after medication.

Postoperative anti-HLA antibody was positive in 2 patients (Cases 3 and 6). In Case 3, DSA was present with an elevated MFI of C7 and DQ7 before retransplantation. In Case 6, DSA was present with an elevated MFI of DQ6.

Typical cases of chronic lung allograft dysfunction after living-donor lobar lung transplantation

The results of ventilation scintigraphy are shown as sequential snapshots by half a minute (Figs 3-5). More radionuclide tracer is...
the late phase represents slower washout indicative of air trapping.

A typical case of unilateral CLAD after LDLLT is shown in Fig. 3. In Case 7, the patient was doing well without any symptom or washout delay in the first postoperative year bilateral LDLLT (Fig. 3B). FEV₁ declined slightly and ventilation scintigraphy showed slower washout of radionuclide tracer indicative of air-trapping in the right lung 12 months after LDLLT (Fig. 3A and C). Her FEV₁ turned to increase only 3 months after the diagnosis of CLAD, but the air-trapping remained (Fig. 3D). This case appeared to correspond to ARAD, and these patients with CLAD respond to azithromycin with an increase of at least 10% in their FEV₁ [11].

In contrast, a case of unilateral CLAD that subsequently developed bilateral CLAD is presented in Fig. 4 (Case 5). In this case, the FEV₁ decreased by 18.0% compared with the baseline and then she was diagnosed with obstructive CLAD 24 months after bilateral LDLLT (Fig. 4A). At the same time, ventilation scintigraphy showed slower washout of radionuclide tracer only in the left lung, which indicated unilateral CLAD (Fig. 4C). In spite of stable FVC, her FEV₁ decreased gradually and the air-trapping remained even after the treatment for CLAD. In addition, ventilation scintigraphy showed air-trapping in the contralateral graft 36 months after the transplantation (Fig. 4D). We considered that CLAD had developed in the bilateral lobes metachronously in this patient.

A paediatric case with CLAD after right single LDLLT is described in Fig. 5 (Case 1). Her postoperative course was uneventful and ventilation scintigraphy showed normal washout (Fig. 5B). However, the FEV₁ declined slightly and ventilation scintigraphy showed slow washout of radionuclide tracer indicative of air-trapping of the graft 1–2 years after LDLLT (Fig. 5A and C). In spite of treatment, her FEV₁ continued to decline and the air-trapping remained (Fig. 5D).

**DISCUSSION**

In this study, we found that 8 of 38 patients (21.1%) who survived more than 3 months after LDLLT developed CLAD. Further, unilateral CLAD development was observed predominantly after bilateral LDLLT. Importantly, the prognosis of LDLLT patients with unilateral CLAD may be better because their unaffected contralateral lobar lung may act as a reservoir. In bilateral LDLLT patients, ventilation scintigraphy could distinguish unilateral BOS from bilateral CLAD by detection of air-trapping. Further, in single LDLLT
patients, we could detect CLAD development by comparison of the current ventilation scintigraphy with the previous one after single LDLLT.

CLAD is a major limitation in the long-term success of lung transplantation. Approximately 60% of lung transplant recipients are affected by CLAD within 5 years after transplantation, and BOS is a major type of CLAD, which consists of approximately two-thirds of all CLAD cases [14]. CLAD after lung transplantation is a great problem that needs to be overcome. Studies on CLAD in cadaveric lung transplantation have been extensively reported [7, 11, 14]. However, there are few reports concerning CLAD after LDLLT [8]. Considering the theory of immunological mechanisms, the prevalence of CLAD after LDLLT should be higher compared with cadaveric lung transplantation because LDLLT requires two differently originated donor lobar lungs in many cases. In fact, to date, there has only been one report by Bowdish et al. [8] that merely described that classical BOS represents 12% of cause of death in survivors 3 months after bilateral LDLLT. In the current study, one-fifth of the patients who survived more than 3 months after LDLLT developed CLAD. We can state that this prevalence of CLAD was not as high as compared with that of cadaveric transplantation reported in the literature [15, 16], and it may be because in most cases of LDLLT, the donors were close relatives to the recipients and the graft lobar lungs suffered less injuries before transplantation, such as less infection and shorter ischaemic time.

Ventilation scintigraphy distinguished between unilateral and bilateral CLAD by signs of air-trapping and revealed that the unilateral development of CLAD was predominant in bilateral LDLLT. We suggest that unilateral development of BOS is a characteristic of LDLLT and may be affected by genetic factors, such as HLA typing mismatches between the recipient and the donor [17, 18]. Environmental factors, such as cytomegalovirus infection [17] or gastro-oesophageal reflux disease [19], which are known risk factors of CLAD in cadaveric donor lung transplantation, may promote the metachronous development of CLAD in the contralateral grafts.

All patients with unilateral CLAD at the time of diagnosis survived past the median follow-up period of 34 months and are still alive. The pulmonary function and general status of 3 of these patients who maintained unilateral CLAD remained in stable condition. Their unaffected contralateral lobar lung may have functioned as a reservoir and contributed to the better prognosis. On the other hand, metachronous CLAD development in the contralateral lobar lung led to exacerbations in 2 patients. One of them
required reperformance of LDLLT due to the deteriorating pulmonary function [12, 13].

Despite the advantages, this potential ability of the unaffacted lobar lung to maintain lung function can mask the decline in FEV₁ of the affected lung and delay the diagnosis of CLAD if the functions of both lobar lungs were not evaluated separately. Due to this potential issue, we focused on the use of ventilation scintigraphy to screen for CLAD after LDLLT. It is widely known that computed tomography does not have enough power to detect early CLAD [20, 21], and even transbronchial lung biopsy is not sufficiently sensitive despite its harmfulness to affected lungs [22, 23]. On the other hand, Shinya et al. [24] reported that ventilation scintigraphy was useful for early detection of CLAD after lung transplantations compared with CT findings. In this study, ventilation scintigraphy was able to detect not only BOS at the same time or before CT findings, but also the decline in FEV₁. Therefore, we recognized that ventilation scintigraphy could be an extremely useful diagnostic tool for detection of early CLAD after LDLLT.

CONCLUSION

BOS developed in approximately one-fifth of the patients who survived more than 3 months after LDLLT. Unilateral CLAD development was predominant after bilateral LDLLT, and its prognosis survived more than 3 months after LDLLT. Short-term outcome in living donors for lung transplantation: the role of preoperative computer tomographic evaluations of isuress and vascular anatomy. Transpl Int 2012;25:732–8.

Conflict of interest: none declared.

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