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CASE REPORT

# Redo living-donor lobar lung transplantation for bronchiolitis obliterans associated with antibody-mediated rejection

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## Summary

Living-donor lobar lung transplantation (LDLLT) is an established therapy for patients with end-stage lung disease, but living-donor lobar lung retransplantation (re-LDLLT) is rarely reported. We previously reported a case of unilateral antibody-mediated rejection after LDLLT in the presence of newly formed donor-specific antibodies against a right-lobe donor. The same patient developed contralateral bronchiolitis obliterans, resulting in bilateral bronchiolitis obliterans, but re-LDLLT was successful. Pathological findings of the explanted lungs were consistent with the clinical course of the patient. One year after re-LDLLT, the patient is doing well without any anti-human leukocyte antigen antibodies. Four lobes from four different donors were transplanted in this patient. The first two lobes were rejected eventually, but the two lobes implanted later presented no signs of rejection at least for 1 year after the transplant. Herein, we report this rare case and compare the clinical course and pathological findings.

## Introduction

Living-donor lobar lung transplantation (LDLLT) is an established therapy for patients with end-stage lung disease [1,2]; however, living-donor lobar lung retransplantation (re-LDLLT) has rarely been reported [2–4]. Antibody-mediated rejection (AMR) has become a topic of interest in the field of lung transplantation [5–8], but it is rarely reported in patients undergoing LDLLT [9]. A relationship between AMR and bronchiolitis obliterans (BO) has been sporadically reported [7,10], but to date, no detailed clinicopathological investigation of an individual patient has been documented.

We previously reported a case of AMR of a unilateral donor lung in the presence of newly formed donor-specific antibodies (DSA) 10 months after LDLLT [9]. In the same patient, the effect of the treatment for AMR was transient and bilateral BO developed, resulting in severe respiratory failure. Two years and 10 months after the first LDLLT, re-LDLLT was finally performed. Herein, we report this rare case with detailed clinicopathological investigation.


 

## Case Report

A 34-year-old woman with idiopathic pulmonary fibrosis underwent bilateral LDLLT. The donor of the right lobe was her husband, and the donor of the left lobe was her mother (Table 1). Pre-operative direct cross-match with the anti-human globulin complement-dependent cytotoxicity (AHG-CDC) cross-match and flow cytometry cross-match (FCXM) methods was negative. No anti-human leukocyte antigen (anti-HLA) antibodies were detected using the LABScreen Single Antigen assay (One Lamda Inc., Canoga Park, CA, USA). Her postoperative course was uneventful, and she remained well after the LDLLT. However, 11 months later, she presented with deteriorating pulmonary function, and screening for anti-HLA antibodies revealed the presence of newly developed DSA (C7 in class I and DQ7 in class II, Table 1). Thus, we performed a direct cross-match between the patient and her 2 donors again. Although the AHG-CDC cross-match was negative, the FCXM (B cell) was positive for the patient and her husband. Based on these findings, we diagnosed AMR caused by de novo DSA. We treated the patient with plasmapheresis and high-dose (1 mg/kg) intravenous immune globulin followed by a single dose of rituximab (375 mg/m$^2$). Screening for anti-HLA antibodies 1 month later still showed DSA with almost the same mean fluorescence intensity (MFI; C7 = 1832, DQ7 = 6192), but the patient's respiratory condition had stabilized (Fig. 1). Monthly intravenous immune globulin (0.5 g/kg) continued to be administered, but the DSA was still present even with an elevated MFI of DQ7 for a year (Fig. 1). Her respiratory state gradually deteriorated, and BOS was diagnosed. More air-trapping was identified in the left lung by ventilation scintigraphy, suggesting unilateral BOS in the left donor graft. Her lung function steadily declined, and she was listed for lung retransplantation 2 years after the LDLLT (Fig. 1). Air-trapping was identified in both lungs by ventilation scintigraphy, suggesting bilateral BOS. Consequently, we decided to conduct a re-LDLLT 10 months after she was listed. At that time, she could hardly walk by herself. Inspiratory and expiratory three-dimensional (3D) CT volumetry showed severe air-trapping in both lungs, but this was more prominent in the left donor lung. The donor of the right lower lobe was her sister, and the donor of the left lower lobe was her brother. Pre-operative direct cross-match using the AHG-CDC cross-match and FCXM methods was negative. No HLA antibodies were detected before re-LDLLT.

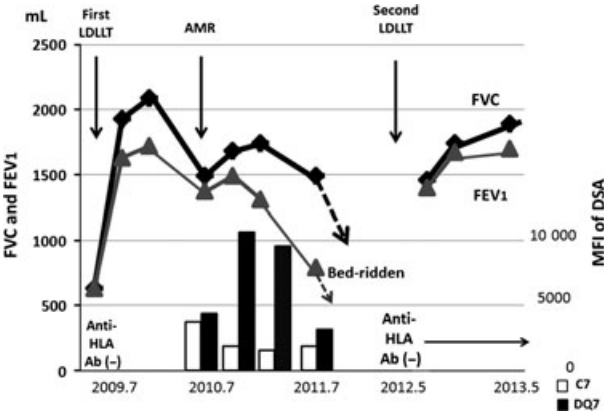


**Figure 1** Trends observed in pulmonary function tests and donor-specific antibodies. AMR, antibody-mediated rejection; DSA, donor-specific antibody; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; HLA Ab, human leukocyte antigen antibody; LDLLT, living-donor lobar lung transplantation; MFI, mean fluorescence intensity.

**Table 1.** HLA typing.

| | A | B | C | DR | DQ |
|---|---|---|---|---|---|
| Recipient (R) | 24, 26 | 35, 61 | 9, 10 | 8, 15 | 6, 8 |
| First LDLLT | | | | | |
| Right donor (R's husband) | 31, 33 | 44, 62 | 7, 14 | 12, 13 | 6, 7 |
| Left donor (R's mother) | 24, – | 35, 52 | 9, 12 | 15, – | 6, – |
| Re-LDLLT | | | | | |
| Right donor (R's sister) | 24, 26 | 52, 61 | 10, 12 | 8, 15 | 6, 8 |
| Left donor (R's brother) | 24, – | 35, 59 | 1, 9 | 4, 15 | 4, 6 |

R, recipient.

The histology of the explanted lungs was that of obliterative bronchiolitis, and a diagnosis of chronic airway rejection was made (Fig. 2a and b). In both lungs, the entire lumen of membranous to respiratory bronchioles was obliterated by scar tissue. The residual smooth muscle wall of the airway and the adjacent pulmonary artery helped identify the obliterated bronchioles. The left lung was more severely affected by the process than the right lung. Mild lymphocytic bronchiolitis and bronchitis were also present.

Intense endothelial C4d deposition was observed in peribronchiolar capillaries adjacent to bronchioles showing obliterative bronchiolitis (Fig. 2c). C4d deposition in peribronchial (Fig. 2d) and pleural capillaries and focal linear C4d staining along alveolar capillaries (Fig. 2e) were noted, as was focal arterial and venous endothelial C4d staining. Overall, the C4d deposition pattern was diffuse and intense in the right lung but weak and focal in the left lung.

The posterior area of the right lung showed an area of airspace filled with diffuse fibrosis (Fig. 2f). The lung architecture was well preserved by elastic tissue stain (Fig. 2g). The appearance was consistent with an organizing pneumonia

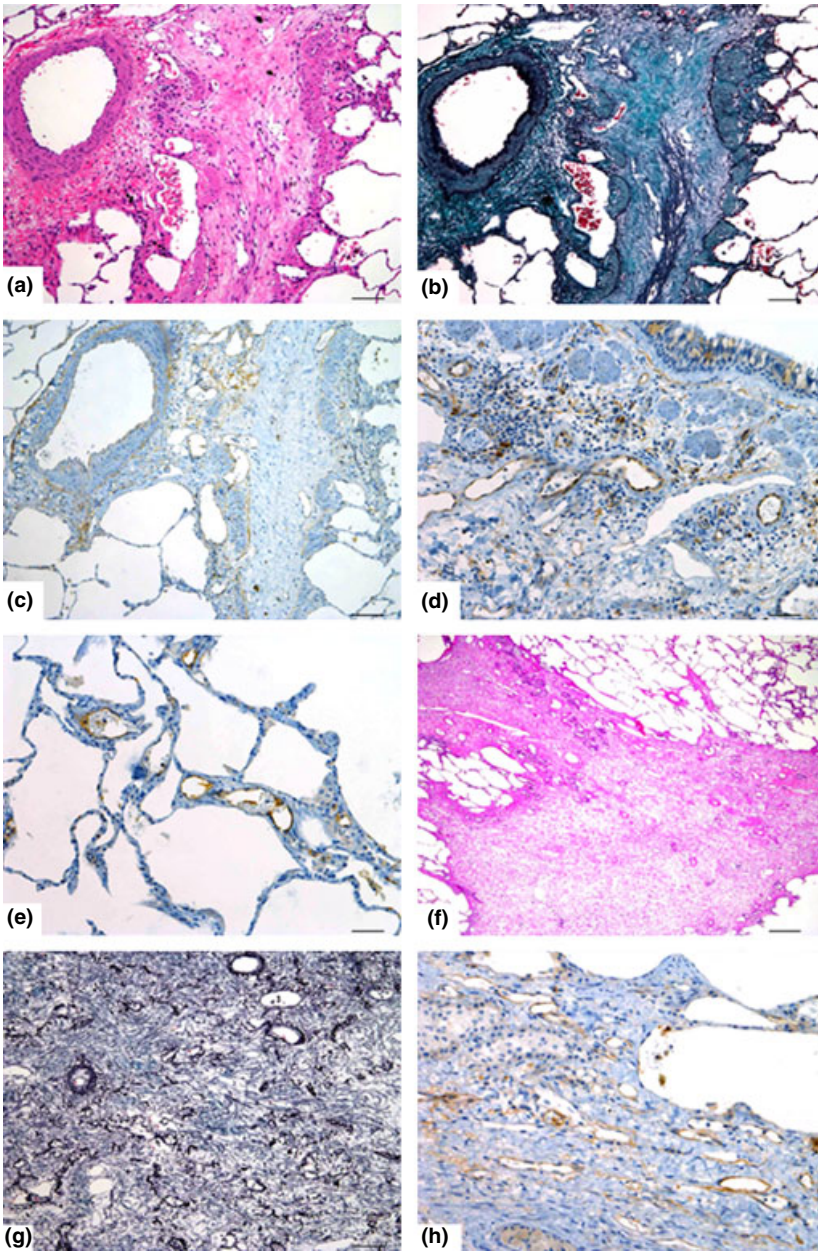


**Figure 2** (a) Chronic airway rejection showing obliterative bronchiolitis. The bronchiolar lumens are totally obliterated by fibrous tissue. Note the residual layer of smooth muscle bundles and the adjacent artery (HE; scale bar = 100 μm). (b) The same specimen as in (a). An elastic tissue stain outlines the obliterated bronchioles. (Elastica-Masson staining; scale bar=100 μm). (c) Endothelial C4d deposition in the peribronchiolar capillaries and artery adjacent to obliterative bronchiolitis from the left lung (C4d immunohistochemistry; scale bar = 100 μm). C4d staining was performed on paraffin-embedded lung tissue using a polyclonal rabbit anti-human C4d antibody (BI-RC4D, Biomedia, Vienna, Austria; 1:50). (d) Intense endothelial C4d deposition in the peribronchial capillaries of the right lung (C4d immunohistochemistry; scale bar = 50 μm). (e) C4d positivity in the alveolar capillary endothelium of the right lung (C4d immunohistochemistry; scale bar = 50 μm). (f) Diffuse airspace fibrosis in the right lung with a corresponding area of diffuse infiltrates on chest CT at the time of elevated donor-specific antibody (DSA) (HE; scale bar = 500 μm). (g) The elastic tissue stain of the corresponding area of Fig. 2f confirms the airspace location of the fibrosis (Elastica-Masson staining; scale bar = 100 μm). (h) C4d deposition in the alveolar septal capillaries in the area of diffuse fibrosis in the right lung and the corresponding area of diffuse infiltrates on chest CT at the time of elevated donor-specific antibody (DSA) (C4d immunohistochemistry; scale bar = 50 μm).


 

pattern, suggesting the organizing stage of acute lung injury (i.e., diffuse alveolar damage, organizing pneumonia). The fibrosis was temporally uniform, which may reflect a recent onset at one specific time of AMR. C4d deposition was diffuse and intense in the area of diffuse fibrosis along the endothelial capillaries in the alveolar septae and arterial or venous endothelium (Fig. 2h).

## Discussion

Lung retransplantation has been reported with acceptable outcomes in selected patients [11–13], but to date, re-LDLLT remains rare worldwide [2–4]. Starnes *et al.*, who have the most experience with such cases, reported seven cases, five of which were re-LDLLT after LDLLT and two of which were re-LDLLT after lung transplantation from deceased donors [2]. Of the former five patients, three underwent single-lobe living-donor retransplantation for primary graft dysfunction, and two received a re-LDLLT for BO 2 and 4 years after LDLLT, respectively. The outcomes of re-LDLLT after LDLLT were disappointing in that 3 of the 5 patients died of infection relatively soon after re-LDLLT. Kozower *et al.* experienced 13 re-LDLLT cases, but only one was re-LDLLT after LDLLT [3]. Introduction of the lung allocation system in the United States has changed the situation of the practice of LDLLT, but re-LDLLT after LDLLT is still an existing challenging operation in countries with severe donor shortage, particularly in Japan.

AMR is rarely diagnosed after lung transplantation and its contribution to chronic rejection still has to be elaborated in future investigations [6–9,12]. In our previous report, AMR was not histologically determined [9]. However, in the current study, the same patient underwent a re-LDLLT, and therefore, we could investigate the explanted lungs to compare the clinical course and pathological findings.

Chronic lung allograft dysfunction is reportedly associated with the pre-existence or development of anti-HLA alloantibodies in lung transplant recipients [14]. Furthermore, the development of anti-HLA antibodies is now recognized as an important risk factor for BOS [15–17]. Because the most important feature of HLA antibodies in lung transplant recipients is donor specificity, DSA is currently considered a target for treatment [8,9]. However, the relationship between DSA and chronic allograft dysfunction, including BOS, still remains to be elucidated [7,10]. In the current case, we could track the clinical course of the recipient from unilateral AMR 1 year after LDLLT to contralateral BOS first detected 17 months after LDLLT and bilateral BOS detected 2 years postoperatively. Of note is the fact that the recipient showed DSA against the right donor and not the left donor and that the left donor lung was more severely affected by BO. This was also proven by the radiological and pathological findings. In contrast, the right donor lung showed more intense and more diffuse C4d staining, consistent with the existence of DSA against the right donor only. DSA was not detected just before re-LDLLT, indicating a possibility that all DSA was absorbed in the right donor lung. These clinicopathological findings, which were unique to LDLLT, might support that HLA antibodies would affect the donor lungs even when they were not donor-specific [18]. Furthermore, interplay between immune responses to HLA and non-HLA self-antigens might be involved [7]. In any case, true pathogenesis of the current patient should be clarified in future.

In conclusion, we discussed a case of re-LDLLT for bilateral BO after unilateral AMR after LDLLT.

## Authorship

CF, M-HA, and DH: designed research/study. CF, M-HA, and DH: performed research/study. CF, M-HA, CN, YT, SM, AA, TS, BT, and DH: collected data. CF, M-HA, YK, and DH: analyzed data. CF, M-HA, SM, AA, TS, and DH: wrote the paper.

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