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Humoral human lung allograft rejection by tissue-restricted non-HLA antibodies

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Abstract

A third of lung recipients have pre-existing antibodies against non-human leukocyte self-antigens (nHAbs) present in the lung tissue. These nHAbs also form *de novo* in about 70% of patients within 3-years following transplantation. Both pre-existing and *de novo* nHAbs can cause murine lung allograft rejection. However, their role in human transplantation remains unclear. We report hyperacute rejection following right lung transplant in a recipient with pre-existing nHAbs. Recipient of left lung from the same donor had uneventful initial course but developed *de novo* nHAbs at three weeks leading to acute humoral rejection. Both were successfully treated with antibody-directed therapies.

Keywords

Antibody/antigen; Rejection; Lung

Damage attributable to the underlying lung disease can expose “sequestered” non-human leukocyte tissue-restricted self-antigens (sAgs) resulting in autoantibody development in the host [1]. We have previously shown that up to one-third of lung recipients with end-stage lung disease have such pre-existing non-human leukocyte antibodies (nHAbs) [2]. Self-antigens, unlike HLA antigens, are non-polymorphic and do not differ between individuals within a species [3]. Self-antigens are normally hidden but ischemia-reperfusion to the allograft can reveal them to the recipient’s immune system. Hence, pre-existing nHAbs in a recipient can bind to sAgs in the allograft following transplantation. The current cross-match technique utilizes donor lymphocytes that do not express tissue-restricted sAgs and,

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therefore, does not detect pre-existing autoantibodies. Therefore, hyperacute rejection may occur due to pre-existing nHAbs, despite a negative crossmatch.

In patients that do not have pre-existing nHAbs, *de novo* nHAbs can develop following lung transplantation [4]. The development of these new antibodies which are of the IgG class takes about 2–3 weeks after antigenic exposure. The *de novo* nHAbs can mediate acute antibody-mediated rejection (AMR) following lung transplantation. Accordingly, we demonstrate, for the first time, development of hyperacute rejection and AMR in two recipients with pre-existing and *de novo* nHAbs, respectively.

Donor

The donor was a brain dead 26yo non-smoker male with a gunshot wound to the head. Chest imaging, bronchoscopy, and lung function were normal. Procurement was performed by two attending thoracic surgeons from Northwestern University and Cleveland Clinic Foundation.

Recipient 1

The right lung recipient was a 53yo female with emphysema and normal pulmonary pressures whom underwent transplantation without cardiopulmonary bypass. Induction immunosuppression consisted of methylprednisolone (500mg) and basiliximab (20mg). Panel reactive HLA antibodies (PRA) were not detected; T- and B-lymphocyte cross-matches were negative. Implantation was uncomplicated with 243minutes of total and 39minutes of warm ischemia. Following reperfusion, the recipient had a PaO_2 of 155mmHg on 30% inspired oxygen (FiO_2). Trans-esophageal echocardiogram revealed normal flow velocities across vascular anastomoses. Thirty-minutes after reperfusion, the allograft became acutely congested and the patient required 100% FiO_2 to maintain a PaO2>70mmHg. Chest radiograph revealed dense infiltrates in the allograft (Figure 1A&B). Contrast computed tomography did not show fat or thrombo-embolism. Transbronchial allograft biopsies on day 1 demonstrated septal neutrophils, diffuse alveolar damage, hyaline membrane formation (Figure 1C), and complement (C4D) deposition (Figure 2B), consistent with antibody-mediated rejection (AMR), as proposed by ISHLT Pathology Council [5]. Furthermore, IgG deposition was noted (Figure 2A). There was no growth of bacteria, fungi, or viruses in the bronchoalveolar fluid. Due to histological features consistent with AMR, despite negative HLA antibodies, we tested for lung tissue-restricted nHAbs on serum collected on the day of transplant, as previously described [2]. The recipient was positive for antibodies to collagen type-V (214μg/ml, normal <106 μg/ml), Kα1-tubulin (160.8μg/ml, normal <145μg/ml) and collagen type-I (14μg/ml, normal <7.3μg/ml) but not non-lung antigens collagen type-II, and IV. The patient was treated with intravenous immunoglobulin (IVIG, 1g/kg), rituximab (375mg/m^2) and bortezomib (1.3mg/m^2). Allograft function improved with resolution of infiltrates (Figure 1D) within 72-hours. Maintenance immunosuppression included tacrolimus (target trough level, 8–12 ng/ml), mycophenolate mofetil (1000 mg twice daily), and prednisone (0.5 mg/kg). At 6-months, the forced expiratory volume in 1-sec (FEV_1) was 65% predicted and she remained on room air. Treatment with antibody-directed therapy for 6-months cleared nHAbs.

Recipient 2

The left lung was transplanted using cardiopulmonary bypass support into a 66yo male with idiopathic pulmonary fibrosis, pulmonary hypertension and left internal mammary artery bypass graft. Cross-match was negative and there were no HLA antibodies. After an uneventful recovery, he was discharged breathing room air on day 18 (Figure 1E). However, on day 24, he presented with hypoxemic respiratory failure and new allograft infiltrates (Figure 1F). Microbial cultures were negative and allograft biopsy revealed AMR (Figure 1G) with IgG and C4D deposition. (Figure 2A). Repeat cross-match and PRA screen for HLA were negative. IgG-nHAbs against collagen type V, I and Kα1-tubulin were negative on transplant. However, *de novo* antibodies to collagen type-V (264μg/ml), Kα1-tubulin (182.6μg/ml) and collagen type-I (19μg/ml), but not collagen type-II, and IV, were identified on day 24. The patient received plasmapheresis, IVIG and rituximab. Allograft function recovered in 72-hours and at 6-months the chest radiograph was normal (Figure 1H); FEV1 was 78% of predicted.

Comment

HLA antibody-mediated hyperacute rejection has significantly decreased following allo-transplantation due to the lymphocytic cross-match. Nevertheless, primary graft dysfunction (PGD) remains a frequent occurrence following lung transplantation [6]. In our series, Recipient 2 had idiopathic pulmonary fibrosis, pulmonary hypertension and required cardiopulmonary bypass for transplantation, all risk factors for PGD [6]. Despite that, Recipient 1 developed PGD but not Recipient 2. We have previously shown that pre-existing nHAbs are present in about a third of lung recipients and these can increase the risk of PGD 7-folds [7]. The time course, histological features, presence of pre-existing nHAbs but not HLA antibodies, lack of other etiologies, and prompt improvement with antibody-mediated therapy are highly suggestive of nHAb-mediated hyperacute rejection that manifested as PGD in Recipient 1. Therefore, it is possible that nHAb-mediated lung rejection is one possible etiology for PGD. The native lung was unaffected likely because sAgs remain sequestered and, therefore, nHAbs cannot bind to the native lung.

The development of *de novo* nHAbs in Recipient 2 is possibly from memory B-cells against sAgs resulting from the end-stage lung disease [8]. These memory B-cells can form nHAbs upon re-exposure to sAgs in the allograft after ischemia-reperfusion. Lung-restricted sAgs can be expressed for over a month following transplantation [9] and development of nHAbs during this time can cause AMR as seen in Recipient 2. Hence, we postulate that Recipient 2 had AMR from *de novo* nHAbs.

Our data suggest that antibodies against lung sAgs can lead to hyperacute or acute humoral rejection that can be treated upon early recognition. This is in agreement with recent murine studies [10]. Testing for these nHAbs should be considered during transplant workup and in patients presenting with either unexplained PGD or post-transplant AMR in the absence of HLA antibodies.

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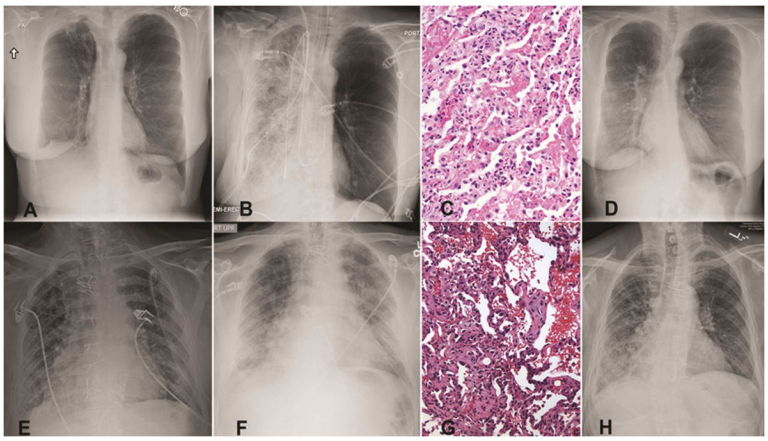

Figure 1.

Clinical course of study patients. A) Pre-transplant chest radiograph of Recipient 1. B) Post-operative imaging showing opacification of the transplanted right lung in Recipient 1. C) Lung allograft biopsy of Recipient 1 with signs of humoral rejection (hyaline membranes, septal neutrophils and alveolar damage). D) Resolution of lung infiltrates in Recipient 1 following treatment. E) Post-operative chest radiograph of Recipient 2. F) Imaging on day 24 showing new left-sided infiltrates in Recipient 2. G) Allograft biopsy of Recipient 2 from day 24 showing antibody mediated rejection. H) Follow-up chest radiograph of Recipient 2 at three months.

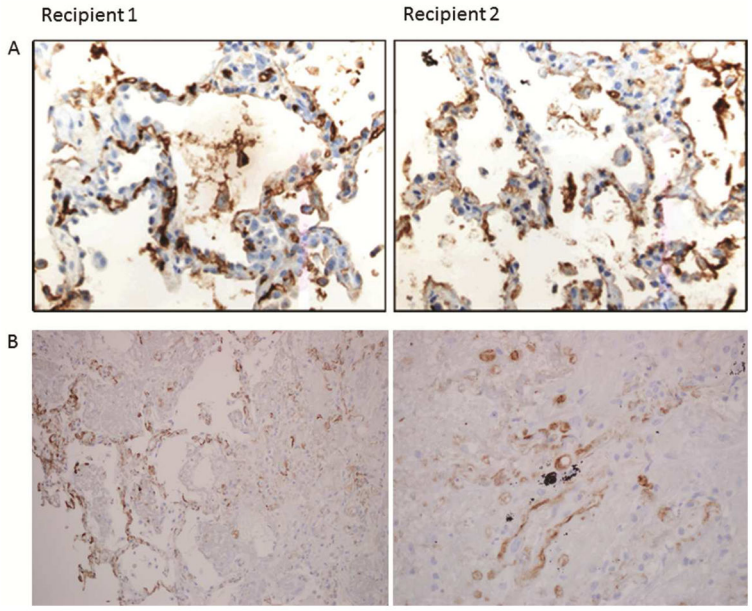

Figure 2.
Evidence supporting the diagnosis of AMR in both recipients. A) IgG deposition. B) Complement deposition.