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Acute antibody-mediated rejection one week after lung transplantation successfully treated with eculizumab, intravenous immunoglobulins and rituximab

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Abstract (150/150 words)

The diagnosis of clinical antibody mediated rejection (AMR) in lung transplantation is based on allograft dysfunction, donor-specific antibodies (DSA) and histopathological findings, but its management remains poorly defined. A 48-year-old female received bilateral lung transplantation, with low-titer preformed class II DSA and a negative flow-cytometry crossmatch at transplant. After an uneventful early post-transplant course, she developed at day 7 rapidly progressive dyspnea, high-titers class I and II DSA, *de novo* positive T and B cell crossmatches with capillary C4d deposits on transbronchial lung biopsy. She was successfully treated with one 600mg dose of eculizumab, three weekly high-dose intravenous immunoglobulins followed by one dose of rituximab at 1 month post-transplantation, without the need for plasmapheresis or T cell depleting agents, resulting in a rapid reversal of the acute AMR episode. In conclusion, this therapeutic approach should be considered and further studied in lung transplant recipients with early acute clinical AMR.

Main text (736/750 words)

Introduction

Mounting evidence exists on the risk of antibody mediated rejection (AMR) after lung transplantation {Roux et al., 2016, Am J Transplant, 16, 1216-28} {Snyder et al., 2013, Chest, 144, 226-233}. In 2016, the International Society for Heart and Lung Transplantation (ISHLT) established for the first time a consensus report which defines and stages clinical and subclinical AMR (acute or subacute) based on the presence of donor specific-antibodies (DSA), specific histopathologic features including neutrophil margination and neutrophil capillaritis and arteritis, capillary C4d deposition and exclusion of other differential diagnoses {Levine et al., 2016, J Heart Lung Transplant, 35, 397-406}. The optimal management of acute AMR remains poorly defined, and is mostly based on previous experience derived from kidney transplantation with plasmapheresis (+/- eculizumab), intravenous high-dose Immunoglobulins (IVIG) and rituximab administration {Chehade et al., 2015, Pediatrics, 135, e551-5} {Chehade and Pascual, 2016, Transplantation, 100, 264-5}.

Case presentation

A 48-year-old female received bilateral lung transplantation because of lymphangioleiomyomatosis with severe obstructive syndrome. Prior to transplantation, she had only one detectable (>500 mean fluorescence intensity (MFI)) low-titer preformed class II DSA (HLA DR17: MFI 1783) by Luminex (Austin, TX), but with a negative flow-cytometry crossmatch. Standard immunosuppressive induction therapy (two 20mg doses of basiliximab at day 0 and 4) was used. After an uneventful early post-transplant course, she developed at day 7 rapidly progressive dyspnea with

hypoxemia (Figure 1A-B). The chest X-ray showed new bilateral interstitial pulmonary infiltrates. Repeat Luminex-assay on post-operative day (POD) 7, 9 and 13 revealed increase of class-I (anti-HLA A24 and B8) and class II (anti-HLA DR17 and DQ2) DSA with *de novo* positive flow-cytometry T and B crossmatches (Figure 1C-D). A transbronchial lung biopsy was performed on POD 13 which showed linear C4d endothelial deposits with minor peri-capillary mononuclear infiltrates and scattered neutrophils (Figure 1E-H). C5b-C9 staining was negative. She was treated on POD 8 with a single 600mg dose of eculizumab preceded with 250mg intravenous methylprednisolone, followed by 3 weekly high-dose IVIG (2g/kg), and on POD28 with one dose of rituximab (375 mg/m^2). Terminal complement blockade (> 97% inhibition) within 48h after eculizumab administration was demonstrated by functional analysis of the complement cascade (classical pathway, alternative pathway and lectin pathway of complement activation). Oxygen requirements rapidly decreased within 24hours after eculizumab administration and she was off oxygen-therapy by day 14 post transplantation (Figure 1A). Circulating DSA progressively decreased below 2000 MFI by POD 41, and remained under 2000 MFI thereafter (Figure 1C). Peripheral B cells are still depleted three years after rituximab administration (<10 B cells/μl). Control transbronchial biopsy at 18 months' post-transplantation did not reveal any residual or active immuno-histological signs for AMR (C4d negative). The patient is currently doing well with a three-year follow-up and without any evidence for chronic lung allograft dysfunction (CLAD).

Discussion

This case illustrates that acute AMR can develop early after lung transplantation in a sensitized recipient who had low-titer preformed DSA prior to transplantation.

Importantly, no hyperacute AMR occurred in this patient. These results highlight the importance to closely monitor DSA and cross-matches in such patients post-transplantation. Interestingly, recent data indicate that de novo DSA appearing within the first 30 days post-transplantation are associated with significantly worse long-term clinical outcomes {Le Pavec et al., 2016, J Heart Lung Transplant, 35, 1067-77}. Moreover, C1q binding and detection of intragraft DSA may be additional useful tools for the diagnosis of AMR, as recently suggested by a retrospective analysis of 51 lung-transplant recipients {Visentin et al., 2016, J Heart Lung Transplant, 35, 1418-1426}.

Eculizumab administration rapidly reversed clinical early acute AMR after lung transplantation, without the need for T-cell depleting agents (e.g thymoglobulin) or plasmapheresis. Histopathological findings from the lung biopsy, performed 5 days after eculizumab, suggested that blockade of the terminal complement pathway could neutralize the consequences of pathogenic DSA (i.e C5b-C9 deposits were not detected), but as expected C5 blockade did not inhibit complement classical pathway activation as shown by the presence of capillary C4d deposits on lung's biopsy, similar to the report by Stegall et al. in kidney transplantation {Stegall et al., 2011, Am J Transplant, 11, 2405-13}. It should be emphasized that, until recently, the treatment of severe acute AMR has been based on immediate removal of DSA by plasmapheresis and on B cells immuno-modulation by IVIG, rituximab or bortozemib therapy {Moll and Pascual, 2005, Am J Transplant, 5, 2611-8} {Chehade and Pascual, 2016, Transplantation, 100, 264-5} {Hachem et al., 2010, J Heart Lung Transplant, 29, 973-80}. Thus, in our case, administration of high-dose IVIG and rituximab, associated with increased baseline maintenance immunosuppression, were likely

critical in the overall successful management and resolution of the acute AMR episode. Interestingly, anti T-cell therapy was not necessary, probably because the rejection process was predominantly humoral and not cellular in its mechanism effector. Finally, the cost-effectiveness of eculizumab as compared to conventional plasmapheresis {Ius et al., 2015, J Heart Lung Transplant, 34, 50-8} still warrants prospective studies based on a multicentric approach due to the low incidence of reported clinical acute AMR.

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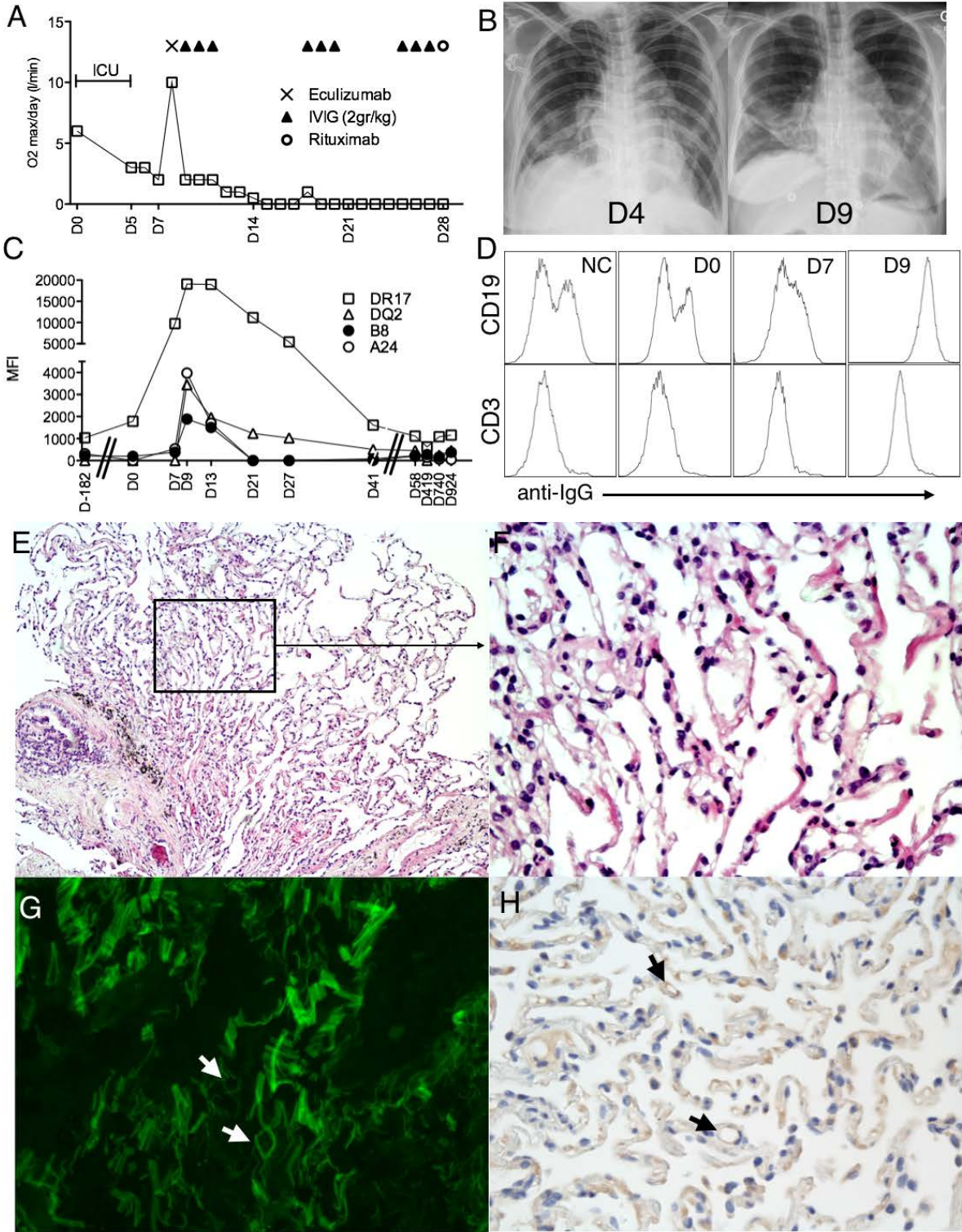
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(A) Oxygen maximal flow rate over time. Treatment with eculizumab (600 mg) on

post-operative day (POD) 8, 3 weekly high-dose intravenous immunoglobulins

(2g/kg)) and rituximab (375 mg/m^2) on POD 28. (B) Chest X-ray at post-operative day (POD) 4 and 9. (C) Donor specific class I and class II antibodies over time. (D) Flow cytometry crossmatches gated on viable (propidium iodide negative) donor CD3 or CD19 cells on POD 0, 7 and 9. Negative control (NC) are third party serum controlled for anti-HLA antibodies co-cultured with donor cells. Lung biopsy performed on POD 13 showing CD3 staining (E, magnification x20), hematoxylin-eosin coloration (F, magnification x40), C4d immunofluorescence on frozen section (G, magnification x40), C4d immunohistochemistry on paraffin section (H, magnification x40). Arrows show C4d deposits on the pulmonary capillaries. Abbreviation: negative control (NC); Day (D); intensive care unit (ICU); intravenous immunoglobulins (IVIG).