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Antibody-mediated Rejection in Lung Transplantation

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Abstract

There has been increasing awareness of antibody-mediated rejection (AMR) as an important cause of graft failure after lung transplantation in recent years. However, the diagnostic criteria for pulmonary AMR are not well defined. All four tenets of AMR in kidney and heart transplantation, graft dysfunction, complement component deposition, circulating donor-specific antibodies (DSA), and histopathologic changes consistent with AMR, are infrequently present in lung transplantation. Nonetheless, the lung transplant community has made important progress recognizing cases of AMR and developing a definition. However, AMR is often refractory to therapy resulting in graft failure and death. In this review, we discuss the progress and challenges in the diagnosis and therapeutic options for pulmonary AMR. In addition, we briefly examine emerging paradigms of C4d-negative AMR and chronic AMR, and conclude that significant progress is needed to mitigate the effects of humoral immune responses after lung transplantation.

Keywords

lung transplantation; graft rejection; donor selection; complement C4d; autoimmunity; HLA antigens

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Conflict of Interest

Hrishikesh S. Kulkarni, Bradford C. Bemiss, and Ramsey R. Hachem declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Lung transplantation remains the only definitive therapy for many patients with end-stage lung disease (1). According to the 2014 International Society of Heart and Lung Transplantation (ISHLT) Registry Report, over 3700 lung transplants were performed worldwide in 2012 (1). However, long-term outcomes remain disappointing, and the median survival is 5.7 years, with graft failure being the leading cause of death (1). Over time, the incidence of chronic lung allograft dysfunction (CLAD) increases, resulting in significant morbidity and mortality and an increase in healthcare resource utilization (2, 3).

Traditionally, graft rejection has been considered primarily as a manifestation of cellular immune responses, and immunosuppressive therapy focusing on inhibiting T-cell responses has made transplantation a clinical reality. However, a role for antibodies has been suspected, and antibody-mediated rejection (AMR) has emerged as an important cause of graft failure (4, 5). While AMR has been widely recognized in heart and kidney transplantation, it has been enigmatic until recently in lung transplantation because of a smaller sample size and challenges identifying the characteristic histology (6, 7). Nonetheless, there is increasing awareness in the transplant community that antibody-mediated graft injury is an important risk factor for CLAD and a potentially reversible cause of graft failure (8–10).

Pathogenesis of AMR

AMR has been best characterized with donor-specific human leukocyte antigen (HLA) antibodies (DSA), but may occur as a result of other donor-specific antibodies (11,12). Recipients may have pre-existing HLA antibodies as a result of pregnancy, previous transfusion, or organ transplantation, or may develop HLA antibodies *de novo* after transplantation (13). Antibodies may develop to either MHC class I antigens or MHC class II antigens (14). Class I antigens are present on nearly every nucleated cell in the body, and are responsible for presenting proteins that have been processed within the cell cytoplasm, including those that may have been altered by viral replication. Class II antigens present processed, exogenous material on antigen-presenting cells such as macrophages and dendritic cells (14). Importantly, pro-inflammatory cytokines may induce the expression of class II antigens on pulmonary endothelial cells (15, 16).

Early experience with AMR was limited to hyperacute rejection. Despite suppressing T-cell activation, some patients developed fulminant, often fatal respiratory failure in the immediate period after transplantation (17). Graft pathology demonstrated hyaline membrane formation, alveolar edema, intra-alveolar fibrin and evidence of vascular injury, such as arteriolar fibrinoid necrosis and intravascular platelet and fibrin thrombi (18). Neutrophilic infiltration was seen in the alveolar septa highlighting a sometimes conspicuous neutrophilic capillary injury (18). Many of these patients were found to have DSA (4, 19). Antigen-antibody complexes and complement component deposition were identified in the capillaries demonstrating that DSA bound HLA on endothelial cells and activated the complement cascade resulting in endothelial cell necrosis and acute lung injury (4).

The advent of solid-phase HLA antibody testing assays has improved the sensitivity and specificity antibody detection before transplantation (20). This allows the use of a virtual cross-match (VXM) to accept potential donors for an allosensitized recipient (21–23). As a result, the incidence of hyperacute rejection has decreased significantly (22, 24). However, patients may still develop acute episodes of graft dysfunction after transplantation that is refractory to conventional immunosuppression, and the pathology in these cases is similar to that in patients with hyperacute rejection (11, 25–27). While initial immunohistochemistry failed to show either IgG, IgM or complement protein C3 in these grafts, many of them had the inactivated complement by-product C4d deposited in the capillary walls, suggesting that complement-mediated endothelial injury played a central role in graft dysfunction (28, 29). Moreover, most of these patients had HLA antibodies, and many were donor-specific (30, 31). Notably, some patients improved with plasmapheresis or other antibody-depleting treatments suggesting that AMR, due to *de novo* DSA or DSA that were undetectable by conventional screening methods, was the cause of graft injury (32).

Importantly, VXM has its limitations; when compared to direct flow cytometry cross-match results in renal transplant recipients, VXM had a sensitivity of 86% (33). In addition, there is an increasing body of literature suggesting that antibodies to non-HLA and to self-antigens (such as antibodies to minor histocompatibility antigens and K-α-1-tubulin) can result in AMR (14, 34). Moreover, the cutoff for avidity of antibodies [measured using mean fluorescence intensity (MFI)] varies among centers, and this introduces additional variability in the detection of HLA antibodies. In a retrospective cohort study of 63 recipients who either had a calculated panel reactive antibody (cPRA) ≥ 50% or DSA, those who had an MFI ≥ 3000 had a significantly higher incidence of AMR compared to those with an MFI < 3000 (35). Hence, a higher cutoff (e.g., 5000) increases the risk of missing potentially pathogenic antibodies on VXM (36, 37). Additionally, HLA-DP antibodies are not accounted for in the cPRA (21, 38).

Risk factors for the development of *de novo* DSA after transplantation are only beginning to be identified (23, 39). One hypothesis is that lung injury and inflammation after transplantation, such as ischemia-reperfusion injury or acute cellular rejection, increase the expression of HLA in the graft and promote leukocyte infiltration into the graft thereby increasing the graft's immunogenicity (14, 40, 41). Indeed, patients have developed *de novo* complement-fixing DSA to HLA-DQ after recurrent acute cellular rejection (42). *De novo* DSA production has been described within 48 hours of a stroke in a patient who did not have DSA in the previous three years leading up to the stroke (43). In addition, community-acquired respiratory viral infection, surgical procedures, transfusion and pregnancy have been identified as potential risk factors for the development of de novo DSA and subsequent AMR. Notably, influenza vaccination did not accelerate *de novo* DSA production or increase the MFI in patients with pre-existing DSA who had undergone solid organ transplantation (7).

Clinical features of AMR

Humoral immune responses may cause a spectrum of clinicopathological findings, but AMR is defined as the presence of DSA, C4d deposition, abnormal histology, and clinically

apparent graft dysfunction (10, 44, 45). Until recently, AMR was believed to occur early after transplantation, either as hyperacute or acute rejection. However, with increasing sensitivity of DSA detection methods and increased awareness, AMR is increasingly recognized beyond the first year after transplantation (46). Additionally, DSA and non-HLA antibodies have been linked with the development of CLAD, raising the possibility of chronic AMR as a distinct phenotype of CLAD (30, 40). AMR may present as hyperacute rejection in patients with pre-existing DSA as early post-operative graft failure. Patients develop severe acute hypoxemic respiratory failure within one hour of completion of the vascular anastomosis, eventually developing multi-system organ failure (32, 47, 48). Hyperacute rejection has been seen after single lung transplantation and after re-transplantation (48–51). While many patients die because of refractory graft failure despite intensive immunosuppression, a minority have survived and done well in the intermediate follow-up period (47, 48, 52).

With the decreasing incidence of hyperacute rejection, acute AMR has become the most common form of humoral rejection. In one of the earliest descriptions of pulmonary AMR that satisfied all criteria proposed by the National Conference to Assess Antibody-Mediated Rejection in Solid Organ Transplantation, the patient developed cough, dyspnea, fever, and hypoxemic respiratory failure requiring mechanical ventilation (44, 45). Multiple DSA were identified and lung biopsies showed diffuse alveolar damage and neutrophilic capillaritis; the patient was treated with intravenous immune globulin (IVIG), plasmapheresis, rituximab and high-dose steroids, which resulted in complete recovery. Subsequently, other groups have identified AMR with variable prevalence, depending on the stringency of the definition. In a retrospective review of 501 transplants, 86 of which developed acute allograft dysfunction of unclear etiology (characterized by dyspnea, hypoxemia and pulmonary infiltrates without infection), only 21 met all four criteria for AMR (10). The incidence of AMR in this study was 4%, and this has been consistent in other studies (37). However, this may underestimate the true incidence of AMR if less severe cases of graft dysfunction are missed or if a clinically occult form of AMR exists. A summary of the clinical characteristics of AMR from single-center cohort studies is shown in Table 1. In general, the clinical signs or symptoms of graft dysfunction are non-specific, but the presence of DSA raises the clinical suspicion for AMR. While acute AMR has become an increasingly recognized form of rejection, there have been no clinical descriptions of chronic AMR to date although the existence of this entity may be appealing because of the recent interest in different phenotypes of CLAD.

Diagnosis of AMR

Despite clear diagnostic criteria in heart and kidney transplantation, there has been no consensus on the definition of AMR in lung transplantation (18, 53). Historically, criteria for the definition of AMR have included: graft dysfunction, histopathologic changes, complement deposition, and the presence of DSA (45). However, in lung transplantation, these criteria may be nonspecific and many patients present with a clinical syndrome that does not meet all criteria. In addition, C4d-negative AMR is increasingly recognized as a form of rejection in kidney transplantation (54). Below, we review the integral components of the definition of AMR, and highlight the issues specific to pulmonary AMR.

Circulating antibody

Over the last decade, the advent of solid-phase assays has allowed an increased sensitivity in the detection of DSA (55). The LABScreen single antigen assay is a sensitive method to detect and identify HLA antibody specificity (55). As the number of reports of pulmonary AMR increase, patterns for pathologic DSA are beginning to emerge. Patients who develop class II DSA or have persistent DSA despite antibody-depleting therapy have worse long-term outcomes after transplantation (10,56). In addition, complement-binding DSA are associated with worse outcomes after kidney and heart transplantation, and preliminary work suggests similar findings in pulmonary AMR although the full impact of C1q-binding DSA in lung transplantation remains to be elucidated (10, 57, 58).

Although circulating DSA is a clinical hallmark of AMR, it is not detectable in some patients who fulfill the other diagnostic criteria for AMR. IgM depletion has been used to detect class I and class II DSA in patients with a high clinical suspicion for AMR in the absence of DSA. In one study, DSA was unmasked in 8 of 11 patients after IgM depletion, and these patients responded well to therapy (59). Alternatively, a “sponge effect”, has been described wherein DSA are detected in the serum only after removal of the graft that was suspected to have AMR (25). Lastly, antibodies to non-HLA antigens may result in AMR (14, 60).

Complement deposition

C4d deposition has been the most contentious criterion in the diagnosis of AMR (61). C4d is produced during the classic complement cascade, which is activated by antigen-antibody complexes. C4d covalently binds to the capillary endothelium, and can be detected for many days after the inciting injury. Hence, unlike its predecessors, C3d or even extracellular C3, it gained immense popularity in the diagnosis of renal AMR, and was used as a surrogate for complement activation in the diagnosis of pulmonary AMR (9, 27, 31, 62, 63). Despite this initial promise, many studies have subsequently shown non-specific C4d deposition in the absence of DSA, or in the presence of concomitant infection, ischemia-reperfusion injury, brain trauma and acute cellular rejection (7). Patterns of C4d deposition used for diagnosis have been variable. Moreover, C4d is seen in a minority of cases with suspected pulmonary AMR (30, 37). The International Society for Heart and Lung Transplantation (ISHLT) Pathology Council proposes that diffuse (>50%) C4d capillary staining be considered “significantly positive” and recommends centers develop their own experience and expertise in interpreting C4d staining (18). However, the inter-reader reliability is poor (64). Furthermore, C4d-negative AMR is recognized as a form of rejection in kidney transplantation (54). In lung transplantation, it is unclear if C4d-negative cases of AMR are distinct from C4d-positive cases or if the difference is due to technical staining and interpretation limitations.

Tissue pathology

Pulmonary capillaritis was initially the hallmark of steroid-resistant acute rejection that responded to plasmapheresis (26). This suggested that capillaritis was the *sine qua non* histopathological finding of pulmonary AMR. However, neutrophils are one of many cell types involved in acute microvascular inflammation, and capillary neutrophilic inflammation

may be regarded as a part of the spectrum of alveolar capillary inflammation. Importantly, its absence should not rule out AMR (18). In addition, neutrophilic capillary inflammation can be non-specific and needs to be distinguished from neutrophilic margination or congestion (53). Lastly, capillaritis may be obscured by the acute lung injury, and is not seen in many cases of AMR (10).

In general, the characteristic pathology in pulmonary AMR has been acute lung injury. The most severe form is diffuse alveolar damage (DAD), but other patterns of lung injury include non-specific interstitial pneumonitis, organizing pneumonia, acute interstitial pneumonitis (7). Of these, one study found DAD to have a positive predictive value of 32.7% and a negative predictive value of 80.6% for DSA-associated graft dysfunction (30). Indeed, the pathology of AMR is generally nonspecific and underscores the need for a multidisciplinary approach to the diagnosis.

Graft dysfunction

There is no uniformity in defining graft dysfunction associated with pulmonary AMR. Inclusion criteria in cohort studies have included symptoms (shortness of breath, fatigue), signs (hypoxemia) and spirometric changes (decreases in FEV1 ≥ 10–20% from baseline). However, a distinct constellation of findings has not been identified. Other important considerations include the possibility of clinically silent AMR. To date, there have been no reports of cases of pulmonary AMR without clinical signs or symptoms.

Treatment of AMR

In general, treatment options for AMR have been imported from other areas in medicine without appropriate clinical trials in transplantation. Indeed, there is a dearth of data in the medical literature describing the management of pulmonary AMR. Importantly, there are no randomized controlled trials and no head-to-head comparisons of different treatment regimens. Furthermore, treatment has generally consisted of multiple concurrent interventions, and it is difficult to make conclusions about the relative efficacy of any intervention because these have been individualized and have depended on the clinical course and the response to other interventions. Below, we detail the different treatments that have been used in pulmonary AMR.

Corticosteroids

Corticosteroids inhibit the early steps in the innate immune response, repress key transcription factors and alter the maturation and differentiation of immune cells (65). High-dose corticosteroids (methylprednisolone 500–1000 mg daily for 3–5 days) have been used for the treatment of AMR in heart transplantation (66). However, in an early study of 40 cases of pulmonary capillaritis, less than half responded to corticosteroids alone (67). Indeed, one of the earliest clinical hallmarks of AMR was steroid-resistance, and steroid monotherapy is essentially never used today. However, high-dose corticosteroids may be useful as part of a multi-drug regimen to expedite resolution of the lung injury.

Plasmapheresis

Given its ability to deplete antibodies and mitigate graft dysfunction refractory to corticosteroids, plasmapheresis is an appealing treatment option in the treatment of AMR after heart and kidney transplantation (68, 69). Plasmapheresis involves removing blood from the circulation and separating plasma from the cellular component; plasma is then discarded, eliminating the offending antibodies, and replaced with either albumin or fresh frozen plasma. Of note, while this removes circulating antibodies, it does not suppress further antibody production. In fact, plasmapheresis alone may result in rebound antibody production, and this requires the concomitant use of agents that suppress antibody production. In pulmonary AMR, plasmapheresis has been shown to reduce DSA and the deposition of C1q, C3, C4d and C5b-9 (70, 71). However, there is significant variability in the number of plasmapheresis sessions used, and various reports have suggested using as few as five and as many as twenty treatments (10, 37, 70).

Intravenous immunoglobulin (IVIG)

IVIG has been the cornerstone of AMR treatment, but the exact mechanism of action is unclear. IVIG may neutralize DSA, inhibit complement activity and cytokine gene activation, and downregulate B-cells. In addition, IVIG may reduce the expression of class II antigens on different cell surfaces (72). IVIG dosing has been highly variable in the literature and the optimal dose is unknown. When used without plasmapheresis, IVIG is typically dosed at 500–2000 mg/kg (8, 37, 72). However, when used in conjunction with plasmapheresis, a lower dose of IVIG is often given after each treatment (100 mg/kg) with a larger single dose at the completion of plasmapheresis (10, 73).

Anti-CD20 antibody

In recent years, rituximab, an anti-CD20 monoclonal antibody, has been used more commonly for AMR (10, 37). The binding of rituximab to CD20 expressed on pre-B-cells and mature B-lymphocytes results in cell lysis and depletion from the circulation, lymph nodes, and bone marrow (74). The optimal dose of rituximab is also unclear.

Proteasome inhibitors

Although rituximab depletes CD20-positive B-cells, it has no apparent effect on plasma cells that are actively producing antibodies. Bortezomib is a monoclonal antibody directed at the 26S proteasome, which is required by plasma cells to degrade misfolded, ubiquinated proteins. Binding the active site of the 26S proteasome activates the protein unfolded response, which is a stress signal leading to plasma cell apoptosis. Typical dosing of bortezomib involves 4 doses of 1.3mg/m^2 (10, 75). The first use of bortezomib in pulmonary AMR resulted in marked clinical improvement, and while the patient developed multiple infections, these were successfully treated, and follow-up transbronchial biopsies showed complete reversal of rejection (75). A similar case report described resolution of AMR, which had been refractory to IVIG, plasmapheresis, and rituximab after treatment with bortezomib (76).

Complement inhibition

The final common pathway of antibody-mediated rejection is endothelial injury by the C5–9 membrane-attack complex (MAC) (29). Therefore, eculizumab, a monoclonal antibody to C5 that prevents the formation of the MAC, is an appealing option for the treatment of AMR (29, 52).

Although multiple treatment options for AMR are available, the optimal combination of treatments and the optimal dosing for any agent are unknown. In addition, each agent has numerous potential side effects, and the risk of infection in a lung transplant recipient with graft dysfunction is high. To date, there is insufficient evidence to adequately guide the treatment of AMR. Therefore, well-designed clinical trials are necessary.

Long-Term Outcomes with AMR

In contrast to acute cellular rejection, AMR generally portends a worse prognosis. In early reports, patients who developed pulmonary capillaritis within the first month of transplant had a 1, 3, and 5 year survival of 82%, 70% and 38%, respectively, whereas those who developed capillaritis beyond the first month had 1, 3 and 5 year survivals of 85%, 83% and 43%, respectively (67). In a more recent case series of patients with AMR, 6 of 21 (29%) died due to refractory AMR, and 13 of the remaining 14 (93%) who did not have pre-existing CLAD developed CLAD during the study period (10). The one year mortality after the diagnosis of AMR in this cohort was 47%, with most patients dying of refractory AMR or CLAD (10). The inability to clear DSA portends a worse prognosis, thus suggesting that chronic, ongoing lung injury in the setting of DSA results in accelerated, refractory graft dysfunction (56). Therefore, although AMR may be a reversible cause of graft failure, there is a high incidence of subsequent CLAD development and a high mortality rate.

Conclusions

AMR is an increasingly recognized form of lung allograft rejection. However, refinement and validation of the diagnostic criteria are necessary to facilitate clinical studies across centers. The role of C4d deposition as a diagnostic criterion is unclear, as many series have reported C4d-negative cases. It also remains unclear whether C4d-negativity in such cases identifies a distinct phenotype of AMR or whether this is due to technical challenges related to staining and interpretation. In addition, although a chronic AMR may exist, evidence supporting this paradigm remains elusive to date. Lastly, although acute AMR may be a reversible form of graft failure, there is a high incidence of subsequent CLAD development and poor overall survival after the diagnosis of AMR. Clearly, additional research is needed to improve outcomes of patients with pulmonary AMR.

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Table 1

Clinical presentation and outcomes of patients with pulmonary antibody-mediated rejection

Study	Sample size	Clinical presentation	Time to AMR from index transplantation	Mortality	Survival duration	CLAD	Time to CLAD
Girnita et al (25)	2 recipients were suspected to have AMR	Both patients had a significant decrease in FEV1	Pt 1: 5 months Pt 2: 2 weeks	NR	NR	2/2	Pt 1: 7 months Pt 2: 2.6 years
DeNico la et al (9)	41 recipients; 5 met criteria for AMR (excluding C4d deposition)	Defined as new hypoxia, FEV1 decline ≥ 10% from prior measurement; present in 9/41 patients. **Only 6/16 DSA + cases had allograft dysfunction**.	NR	NR	NR	NR	NR
Jackup s et al (70)	8/9 recipients had 11 AMR episodes *	NR	Range: 11 days – 71 months	Died – 2/8 ReTx – 2/8	Died – 2/8 in < 1 month; others NR	NR	NR
Daoud et al (8)	14/62 recipients had at least one marker for AMR; 2/3 met all criteria	Acute dyspnea, new radiographic abnormality or significant decline in FEV1	Range: 1–34 months	Died – 5/10 patients with possible/probable AMR	1–704 days after diagnosis of AMR	NR	NR
Lobo et al (30)	11/44 recipients developed AMR (DSA + graft dysfunction + no coinfection); C4d not necessary	All patients with AMR had ‘progressive graft dysfunction’ (definition not specified)	Median time: 63.8 ± 51.9 weeks	Pts with DSA who died at – 1 yr – 1/13 3 yr – 4/11	Mean: 835 days post-Tx in pts with DSA	21/44 total; all pts with AMR went on to BOS	NR
Witt et al (10)	21/484 recipients had AMR	Dyspnea, hypoxemia and pulmonary infiltrates, no infection; 14/21 required invasive mechanical ventilation	Median: 258 days (mean: 364±402 days); 7/21 patients developed AMR after first year	Died-15/21; 6/15 died during index admission	Median survival time: 593 days post-Tx	13/14	Mean: 389 ± 137 (median : 114) days after AMR diagnosis
Otani et al (37)	9/255 recipients had AMR (did not require C4d for diagnosis)	4/9 – decline in gas exchange, radiologic infiltrates after period of stability 3/9 – worsening spirometry 2/9 – rapidly worsening shortness of breath	Only looked at diagnosis of AMR within 12 months after Tx. Range: 8– 214 days	Died – 6/9	79–610 days after Tx	7/93 – BOS 4 - RAS	NR
Kim et al (35)	11/126 recipients developed AMR	All pts meeting criteria for AMR had “allograft dysfunction” (definition not specified)	1–1117 days	NR	NR	NR	NR

* The study by Jackups et al was in pediatric transplant recipients and included re-transplants.

AMR: antibody-mediated rejection; BOS – bronchiolitis obliterans syndrome; DSA: donor-specific antibodies; FEV1 – volume exhaled during the first second of a forced expiratory maneuver; NR: not reported; pt: patient; RAS: restrictive allograft syndrome; ReTx: re-transplantation; Tx: transplantation;