Antibody-Mediated Rejection in Lung Transplantation: Fable, Spin, or Fact?

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The lung transplant community continues to struggle with the diagnosis and management of antibody-mediated rejection. The four diagnostic tenets of donor-specific antibodies, C4d staining, histopathologic changes, and allograft dysfunction, which were largely derived from the early Banff meetings on renal transplantation, have somewhat arbitrarily been applied to lung transplantation. With the passage of time, it is increasingly apparent that merits of these diagnostic pillars are less robust in lung transplantation. In this article, we summarize some of the controversies and challenges surrounding the diagnosis of antibody-mediated rejection in lung transplantation.

Keywords: Lung transplantation, Antibody-mediated rejection, Humoral rejection, Chronic lung allograft syndrome.

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C enturies ago, a Hans Christian Andersen fairy tale, the “Emperor’s New Clothes,” described the disconnection between what we think we know and what we actually know. More recently, former U.S. Secretary of Defence, Donald Rumsfeld, applied a contemporary spin describing “known knowns,” known unknowns” and the “unknowns unknowns” (1). Both are apposite when we consider antibody-mediated rejection (AMR) in lung transplantation. In this article, we propose that an over-reliance on accepting diagnostic and therapeutic paradigms from the nonpulmonary solid organ transplant setting has muddied our thinking on how we should approach AMR in lung transplantation. In particular, the apparently rock-solid diagnostic tenets inherent to the Banff classification of AMR in renal transplantation (Table 1) may not be directly applicable to the lung allograft (2).

The humoral theory of rejection, put simply, states that alloantibodies against donor-specific human leukocyte antigen (HLA) drives complement activation, and the resulting tissue deposition of C4d confirms the diagnosis of AMR. Acute and chronic AMRs are clearly vascular phenomena in renal transplantation, yet many of the truly problematic chronic lung allograft dysfunction syndromes are airway and parenchymally based, without obvious vascular explanations or links (3, 4). To better understand AMR, we need to dissect the pathways through which immune cells are switched on to produce antibodies specifically targeted against lung epitopes, resulting in tissue damage and impaired pulmonary function. Only through an improved understanding of the immunobiology of lung AMR can we better apply our diagnostic tools with a view to delivering appropriately targeted therapeutics. We cannot simply accept that lung AMR must equal kidney AMR. It is time to take a critical view of the evidence behind the definitions of lung AMR.

DEFINING THE ANTIGENIC TARGET WITHIN THE LUNG ALLOGRAFT

After transplantation, the recipient’s immune response is largely targeted against nonself major histocompatibility complex antigens, encoded by the HLA class I and II genes, present within the lung allograft (5). The presence of anti-HLA donor-specific antibodies (DSA), produced by B cell or plasma cells, has been associated with both acute and chronic allograft dysfunctions (6–11), although the evidence in lung transplantation is not as robust as that in renal and cardiac transplantation (12, 13).

The alloreactive antibody response is determined not only by the antigenic load, or HLA expression, within the lung allograft, both with regard to initial B-cell priming but also subsequent complexing of antibody with antigen. Historical immunology dogma states that although HLA class I expression is universal, HLA class II expression is more selective and may not actually be present within normal lung tissue, although may be upregulated in lung injury (14) or in allografts with bronchiolitis obliterans syndrome (15). The presence of DSA is not sufficient to automatically imply injury to the allograft. In contrast, DSA may not be detectable within the blood during acute episodes of AMR, if the DSA is completely absorbed within the lung allograft complexed to its cognate ligand. Further studies are required to confirm: (i)
TABLE 1. Proposed stages of antibody-mediated rejection in renal transplantation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Term</th>
<th>Diagnostic criteria</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Latent AMR</td>
<td>Circulating DSA only (no histologic changes or graft dysfunction)</td>
</tr>
<tr>
<td>II</td>
<td>Silent AMR</td>
<td>Circulating DSA and immunologic evidence of complement activation (C4d positive)</td>
</tr>
<tr>
<td>III</td>
<td>Subclinical AMR</td>
<td>Circulating DSA, immunologic evidence of complement activation, and histologic pathology</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical AMR</td>
<td>Circulating DSA, immunologic evidence of complement activation, histologic pathology and graft dysfunction</td>
</tr>
</tbody>
</table>

Modified from Takemoto et al ((2)).

AMR, antibody-mediated rejection; DSA, donor-specific antibodies.

The lung transplant recipient presenting with an otherwise unexplained drop in lung function, anti-HLA DSA, a neutrophilic capillaritis and positive C4d staining, fulfils the Banff criteria, and is highly likely to have AMR as the cause for graft dysfunction. In such cases, a diagnosis of “Probable
AMR” is suggested (Table 2). In our clinical experience, this scenario is uncommon. Partially related to the factors discussed above, the more common clinical presentation is of a patient with an unexplained drop in pulmonary function and DSA. In these cases, lung biopsy does not suggest an alternative diagnosis, yet also does not demonstrate features that are said to represent AMR. The absence of confirmatory histology should not automatically rule out the diagnosis of AMR, and the term “Possible AMR” is appropriate. Of note, the Luminex screen for the presence of DSA may be falsely negative if the antibody is completely adsorbed within the allograft. Future epidemiologic, diagnostic, and interventional studies of AMR in lung transplantation should include patients with both “probable” and “possible” AMR.

**THERAPIES**

The AMR therapies are numerous, but basically only the subject of uncontrolled case series in the setting of lung transplantation. Solid clinical evidence of efficacy is not available—particularly in terms of long-term graft outcomes. Reported treatment approaches typically involve a combination of intravenous methylprednisolone, intravenous immunoglobulin, Rituximab, and plasma exchange (4, 6, 7, 11, 26–28). Clinical responses and impact on DSA are variable, with a suggestion that if treatment does not reduce the MFI of the DSA, then clinical resolution is less likely (7). Mycophenolate mofetil, antithymocyte globulin, intravenous immunoglobulin, Rituximab, Bortezomib, Eculizumab, and plasma exchange are complex, expensive medicines or procedures with significant associated morbidity—particularly when used in combination (29, 30).

**FUTURE DIRECTIONS**

The horse must come before the cart. Before any discussion regarding the treatment and management of AMR, the lung transplant community needs to develop a robust and universally agreed definition of AMR in lung transplantation. Such a definition must incorporate some degree of recognition of the following factors:

- the role of both HLA and non-HLA DSA;
- complement-dependant and complement-independent pathways of antibody-associated immune activation;
- current limitations regarding the use of solid phase assays, such as Luminex, in defining anti-HLA and other DSA;
- pathologic correlates of AMR, with less reliance on C4d staining as a major determinant for the diagnosis of AMR;
- the presence of both clinical and subclinical phenotypes of AMR;
- long-term complications related to DSA and their association with the different chronic lung allograft dysfunction phenotypes, for example, bronchiolitis obliterant syndrome and the restrictive allograft syndrome.

Importantly, we need further epidemiologic and observational studies that describe the impact and clinical course of patients sensitized with DSA before transplantation as well as those who develop de novo DSA after lung transplantation.

**CONCLUSION**

Let us be clear—the emperor’s shiny expensive lung transplant AMR clothes are not actually real to a discerning practicing lung transplant clinician. The renal transplant paradigm of Takemoto’s has not proven itself to be easy to apply to lung transplant, with the expensive suggested diagnostic and therapeutic strategies falling well short in terms of useful clinical outcomes. To date we have certainly not remotely seen value for clinical dollars invested in our AMR “wardrobe.” In lung transplant AMR, little is known and much remains unknown.

**REFERENCES**


**TABLE 2.** Proposed stages of acute antibody-mediated rejection in lung transplantation

<table>
<thead>
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<th>Stage</th>
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<tr>
<td>I</td>
<td>Possible AMR</td>
<td>Circulating DSA and graft dysfunction</td>
</tr>
<tr>
<td>II</td>
<td>Probable AMR</td>
<td>Circulating DSA, C4d positive histologic pathology (including noninfection related interstitial neutrophilia) and graft dysfunction</td>
</tr>
</tbody>
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AMR, antibody-mediated rejection; DSA, donor-specific antibodies.


