Antibody Mediated Rejection (AMR) in LUNG TRANSPLANT Recipients

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Overview

1. Does AMR Exist in Lung Transplant?
2. What Might AMR Look Like in Lung Transplant?
3. How might this fit into our current schematic of rejection?
Does AMR Exist in Lung Transplant?

• Well recognized as cause of allograft dysfunction in other solid organ transplants
  – esp. Kidney and Heart
# ISHLT Heart AMR Nomenclature

<table>
<thead>
<tr>
<th>Grade</th>
<th>Consensus Definition</th>
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<tbody>
<tr>
<td>pAMR 0</td>
<td><strong>Negative for Pathologic AMR:</strong> both histologic and immunopathologic studies are negative.</td>
</tr>
<tr>
<td>pAMR 1 (H+)</td>
<td><strong>Histopathologic AMR Alone:</strong> histological findings present and immunopathological findings negative.</td>
</tr>
<tr>
<td>pAMR1 (I+)</td>
<td><strong>Immunopathologic AMR Alone:</strong> histological findings negative and immunopathological findings <strong>positive.</strong></td>
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<tr>
<td>pAMR 2</td>
<td><strong>Pathologic AMR:</strong> Both histologic <em>and</em> immunopathologic findings</td>
</tr>
<tr>
<td>pAMR 3</td>
<td><strong>Severe Pathologic AMR:</strong> rare cases of severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis and marked edema.</td>
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</tbody>
</table>

Does AMR Exist in Lung Transplant?

• Well recognized as cause of allograft dysfunction in other solid organ transplants
  – esp. Kidney and Heart
• Increasing evidence to support role for antibodies and complement mediated rejection
• No consensus definition exists
## Classification and Grading of Pulmonary Allograft Rejection

<table>
<thead>
<tr>
<th>Category</th>
<th>Grading</th>
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<tbody>
<tr>
<td><strong>A: Acute (cellular) rejection (ACR)</strong></td>
<td>0—none</td>
</tr>
<tr>
<td></td>
<td>1—minimal</td>
</tr>
<tr>
<td></td>
<td>2—mild</td>
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<tr>
<td></td>
<td>3—moderate</td>
</tr>
<tr>
<td></td>
<td>4—Severe</td>
</tr>
<tr>
<td><strong>B: Airway inflammation</strong></td>
<td>0—none</td>
</tr>
<tr>
<td></td>
<td>1R—low grade</td>
</tr>
<tr>
<td></td>
<td>2R—high grade</td>
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<tr>
<td></td>
<td>X—ungradeable</td>
</tr>
<tr>
<td><strong>C: Chronic airway rejection— OB</strong></td>
<td>0—absent</td>
</tr>
<tr>
<td></td>
<td>1—present</td>
</tr>
<tr>
<td><strong>D: Chronic vascular rejection</strong></td>
<td>Not graded</td>
</tr>
</tbody>
</table>

Stewart et al. *JHLT* 2007; 26 (12): 1229-1242
Does AMR Exist in Lung Transplant?

• “The presence of serum anti-HLA antibodies and the deposition of complement in alveolar tissue after transplantation suggest a role for humoral immune responses in lung.”

Stewart et al. *JHLT* 2007; 26 (12): 1229-1242
What might AMR look like in LTX?

• Hyperacute Rejection (preformed Antibodies)
• Acute Humoral Rejection
• Mediator for BOS / CLAD
Hyperacute Rejection

- Early Graft dysfunction (in the first 24 hours) associated with preformed HLA antibodies
- Well recognized to cause graft dysfunction as a result of Donor-Directed Antibodies
Acute AMR

• Role of humoral factors in Acute Rejection remains controversial

• No concordance between pathologists in grading AMR:
  – ?Capillaritis
  – ?C4d staining (IHC or IF)
Capillaritis

The Histopathology of Lung Allograft Dysfunction Associated With the Development of Donor-specific HLA Alloantibodies.
C4d Deposits

The Histopathology of Lung Allograft Dysfunction Associated With the Development of Donor-specific HLA Alloantibodies.
Humoral Factors in BOS

• *de novo* development of DSA after LT increases risk of BOS
  – Incidence of DSA development 10% - 56%
Donor-Specific Antibodies

- Negative cross-match
- 65/116 (56%) developed DSA

DSA Class

- Class I: 41
- Class II: 10
- Class I & II: 14

52/65 developed DSA in 90 days

DSA depletion and BOS

DSA clearance and survival

Hachem et. al. *JHLT.* 2010; 29(9):973-80.
Possible Interactions in Antibody Mediated Rejection in Pulmonary Allograft

- Sensitization
- *PGD
- HLA mismatch
- DSA
  Or
  Auto-Antibodies
- Hyperacute Rejection
- Acute AMR
- BOS / CLAD
How might this fit into our current schematic of rejection?
Rejection in Lung Transplant

Relative incidence of rejection by time post Lung Transplant.

- BOS
- Acute cellular rejection
- Hyperacute rejection

Potential Relationships between AMR, ACR, and Pulmonary Allograft Dysfunction
ACR and HLA Antibodies

Moderate ACR = dominant pattern of rejection coinciding with development of anti-HLA antibodies

The Histopathology of Lung Allograft Dysfunction Associated With the Development of Donor-specific HLA Alloantibodies.
Acute lung injury = the 2nd most common pattern seen with development of anti-HLA alloantibodies

The Histopathology of Lung Allograft Dysfunction Associated With the Development of Donor-specific HLA Alloantibodies.
Histologic Features of TBBx in Patients With and Without Anti-HLA Antibody (HLA-AB) and High-grade Acute Cellular Rejection (>=A2)

The Histopathology of Lung Allograft Dysfunction Associated With the Development of Donor-specific HLA Alloantibodies.
Is there a way to put it all together?
## Possible Proposal for Stages of AMR in Pulmonary Allograft

<table>
<thead>
<tr>
<th>Stage</th>
<th>Circulating Antibodies</th>
<th>Lung Biopsy Pathology</th>
<th>Graft Dysfunction</th>
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</thead>
<tbody>
<tr>
<td>I: Latent</td>
<td>YES</td>
<td>NORMAL</td>
<td>NO</td>
</tr>
<tr>
<td>II: Silent</td>
<td>YES</td>
<td>+C4d deposition (NO histologic changes)</td>
<td>NO</td>
</tr>
<tr>
<td>III: Sub-clinical</td>
<td>YES</td>
<td>+ C4d deposition + tissue pathology</td>
<td>NO</td>
</tr>
<tr>
<td>IV: Clinical</td>
<td>YES</td>
<td>+ C4d deposition + tissue pathology</td>
<td>YES</td>
</tr>
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Stewart et al. *JHLT* 2007.; 26 (12): 1229-1242
HALT Study
(HLA Antibodies in Lung Transplantation)

• Multicenter Study
• Development of HLA antibodies after Lung Transplant Recipients
  – Consensus HLA testing
  – Pathologic review of C4d staining
  – Assessment of other clinical data suggesting graft dysfunction in association with these HLA and pathologic findings…
Summary

1. Does AMR Exist in Lung Transplant? **YES**
2. What Might AMR Look Like in Lung Transplant?
   - Hyperacute Rejection
   - Acute AMR
   - BOS / CLAD
3. How might this fit into our current schematic of rejection?
   - Will need grading / staging system, but not in isolation of other forms of rejection
   - More research is needed....