Pathology of Lung Transplantation

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Major topics in this presentation

• Pathologic grading of rejection:
  The new ISHLT classification system.
• Antibody-mediated rejection
• The pathogenesis of obliterative bronchiolitis/chronic rejection.
Lung Transplant Pathology


Lung Transplant Pathology

Stewart S, et al., Revision of the 1995 working formulation for the standardisation of nomenclature in the diagnosis of lung rejection
(In Press; The Journal of Heart and Lung Transplantation)
The diagnosis of rejection is one of exclusion; infection and other lesions must be ruled out.

At least 5 pieces of alveolar parenchyma are necessary for a reliable diagnosis.

At least 3 h&e stained slides from 3 levels in the block and trichrome (connective tissue) stain must be reviewed.
Lung Transplant Pathology: Revised ISHLT grading

A. Acute Rejection
   0 - None
   1 - Minimal
   2 - Mild
   3 - Moderate
   4 - Severe
   X - Ungradeable

B. Airway Inflammation (Bronchioles only)
   0 – None
   1R – Low grade
   2R – High grade
   X - Ungradeable
Acute Lung Rejection

A0  No infiltrates
A1  Rare circumferential perivascular infiltrates, 2-3 cells thick; no eosinophils or endothelialitis.
A2  Perivascular infiltrates readily seen at low magnification; eosinophils and endothelialitis are frequent.
A3  Infiltrates extend into alveolar septae.
A4  Diffuse infiltrates and alveolar injury.
AX  Fewer than 5 good pieces of alveolar parenchyma
Infection in the Lung Allograft

- **FUNGAL**: Candida, Aspergillus, Cryptococcus
- **VIRAL**: CMV, Adenovirus
- **Pneumocystis carinii**: Granulomatous; cysts may be very rare
- **BACTERIAL**
Other pathology in the lung graft

- Infection
- Reperfusion injury
- Aspiration pneumonia
- Allergic Bronchopulmonary Aspergillosis
- Bronchiolitis Obliterans - Organizing Pneumonia
- Bronchus-associated lymphoid tissue
Other pathology in the lung graft (continued)

• Drug toxicity (Rapamycin – org. pneumonia)
• Post-transplant lymphoproliferative disease
• Biopsy sites
• Recurrent native disease: Sarcoid, Langerhans cell histiocytosis, lymphangioleiomyomatosis, BAC, DIP.
Acute Lung Rejection: Airway Inflammation (Bronchioles only)

**B0** – No bronchiolar inflammation

**B1R** (low grade small airway inflammation) – Submucosal mononuclear cells with occasional eosinophils. May be circumferential. No epithelial damage or intraepithelial infiltration.

**B2R** (high grade small airway inflammation) - Eosinophils and plasmacytoid cells present with intra-epithelial inflammation and epithelial necrosis.

**BX** - Ungradeable
Chronic Lung Rejection: Airways and Vessels

**C. Chronic Airway Rejection – Obliterative Bronchiolitis**

*C0*: No obliterative bronchiolitis

*C1*: Obliterative bronchiolitis is present

**D. Chronic Vascular Rejection - Accelerated Graft Vascular Sclerosis (Arteries and/or veins)**
Is there humoral rejection in lung transplants?

- Hyperacute rejection not yet defined.
- Humoral rejection not yet defined.


No IgG, IgM or C3c demonstrated in vessels, alveoli or interstitium in 90 biopsies from 55 patients.
Stages of humoral response to an organ graft

I. Latent – Circulating antibody (to HLA or other endothelial antigens)

II. Silent – Circulating antibody + C4d deposition

III. Subclinical – Circulating antibody + C4d + tissue pathology

IV. Humoral rejection – Circulating antibody + C4d + tissue pathology + graft dysfunction

Circulating anti-HLA and patchy C4d deposition in graft with low sensitivity and low specificity.


Sensitized patients have more post-tx ventilator days than do non-sensitized patients.

Lung: Humoral rejection

C4d deposition is a stronger predictor of septal capillary necrosis and clinical acute rejection than are C1q, C5b-9, or Ig.

C4d and C1q are deposited in bronchial walls in Bronchiolitis Obliterans Syndrome.

Lung: Humoral rejection

C4d staining may be positive in variable and non-specific patterns.

Bronchiolitis Obliterans

- Toxic fumes
- Respiratory infections
- Connective tissue disorders
- Following bone marrow or lung transplantation
Post-transplant Obliterative Bronchiolitis

- 50 – 60% of patients surviving 5 years.
- Median time to diagnosis is 16 – 20 months.
- Bronchiolitis Obliterans Syndrome (BOS): A clinical classification based on % decrease in FEV-1 and FEV 25-75 compared with baseline.

OB: Alloimmune-dependent factors

• Acute rejection, particularly if high grade or persistent or late-onset.
• ?Lymphocytic bronchitis/bronchiolitis
• HLA mismatch
• Development of anti-HLA antibodies
OB: Alloimmune-independent factors

- Cytomegalovirus infection
- Other lung infections (RSV, parainfluenza, influenza, adenovirus, rhinovirus)
- Chemical injury from aspiration with gastroesophageal reflux disease
OB: Alloimmune-independent factors

- Trigger the innate immune system (PMN, monocytes, eosinophils, NK cells, cytotoxic cells, dendritic cells) via Toll-like receptors.
- Hyporesponsiveness with polymorphisms for TLR-4 receptor (Asp299Gly or Thr39911) leads to decreased rates of acute rejection and BOS after lung transplantation.

Innate immunity is linked with adaptive immunity.
OB: Cells

- T-cells
- Neutrophils
- Monocytes/macrophage
- Fibroblasts & endothelial cells

Murine heterotopic tracheal transplant model:

T-cells required (CD8 > CD4); B-cells play a minor role; neutrophils are not required.

Cautions: This model is not a functional airway and is not primarily vascularized and human OB is primarily a disease of small airways.
OB: Cytokines and Chemokines

• T-cell growth factors – IL2, TNFα,β, IFNγ, IL-12, IL-6.
• Chemokines – CCL2, CXCL2, 10, 11, CXCR2, RANTES.
• Cytolytic effectors – perforin, granzyme.
• Remodeling – matrix metalloproteininases, ET-1, PDGF, FGF, IGF-1, TGF-β
Post-transplant Obliterative Bronchiolitis

A fibro-obliterative response to alloimmune factors and non-immune factors engaging both the adaptive and innate immune systems.