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)

Lung Transplant Pathology

• 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 Vasculopathy
(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

Lung: Humoral rejection

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.


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


Lung: Humoral rejection

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


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.


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 Thr399I11) 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, IFNγ, IL-12, IL-6.
- Chemokines – CCL2, CXCL2, 10, 11, CXCR2, RANTES.
- Cytolytic effectors – perforin, granzyme.
- Remodeling – matrix metalloproteinases, 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.
The Pulmonary Pathology of Iatrogenic Immunosuppression

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The indications for iatrogenic immunosuppression

- Autoimmune/inflammatory disease
- Chemotherapy for malignant neoplasm
- Bone marrow and solid organ transplantation

The spectrum of subsequent disease

- Infection
- Therapy-related lung disease
- Recurrence of original disease
- Graft versus host disease
- Post immunosuppression immunoproliferative disease
- Transplant rejection

Lung Disease Timetable Post BMT

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Disease</th>
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<tbody>
<tr>
<td>0-1</td>
<td>Acute GVHD</td>
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<tr>
<td>2-3</td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td>4-5</td>
<td>Acute rejection</td>
</tr>
<tr>
<td>6-7</td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td>8-9</td>
<td>CMV infection</td>
</tr>
<tr>
<td>10-12</td>
<td>Opportunistic infection</td>
</tr>
<tr>
<td>13-18</td>
<td>Transplant rejection</td>
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</tbody>
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A 58 year old woman renal transplant recipient presented with symptoms of acute pneumonia and meningoencephalitis.

Chest imaging showed diffuse bilateral infiltrates. Bronchoscopic evaluation was terminated before biopsy, and bronchial washings failed to grow any organisms.

Despite broad spectrum antibiotics and intensive support, she expired several days after admission.

He was treated with aerosolized ribaviran, but his infiltrates progressed. A surgical lung biopsy was performed.
Diagnosis
Category 1 Infection
Acute Pneumonia and Meningoencephalitis caused by Free-living Amoebae
Acanthamoeba spp. vs Balamuthia mandrillaris


<table>
<thead>
<tr>
<th>Noncomital</th>
<th>Opportunistic</th>
<th>Comm. Acquired or Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial/mycobacterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
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<td>Viral</td>
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<td>Parasitic</td>
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A 68 year old woman presented with breathlessness and hypoxemia. Five months earlier she had been diagnosed with large B cell lymphoma (CD20 positive) and was treated with decadron and Rituxan.

One month after beginning therapy, she complained of cough and shortness of breath. She was found to be neutropenic and was begun on antibiotic therapy (vancomycin) for presumed pneumonia.

Her neutropenia improved, but her cough and breathlessness progressed. She was begun on azithromycin and bronchodilators without improvement.

A surgical lung biopsy was performed.
Case 2: Diagnosis

Category 2: Therapy-associated disease

Cellular interstitial pneumonia with small airways disease and evidence of constrictive bronchiolitis. There are subacute arteriopathic changes possibly related to therapy.

The favored interpretation for the patient’s interstitial pneumonia is drug effect related to Retuxin therapy.

3 Main Patterns of Drug Reaction

- ALI/EP-like
- NSIP/HSP-like
- Fibrosis
Rituximab is a murine monoclonal antibody directed against CD20. FDA indications include relapsed (or refractory) low grade or follicular, CD20 positive B cell lymphomas. May be used in combination therapy with other agents in higher grade CD20 positive lymphomas.

Pulmonary toxicity related to rituximab is reported but uncommon.

Interstitial pneumonia associated with rituximab may be severe.


The spectrum of subsequent disease

- Infection
- Therapy-related lung disease
- Recurrence of original disease
- Graft versus host disease
- Post immunosuppression immunoproliferative disease
- Transplant rejection

A 58 year old woman presented with progressive respiratory difficulty and reticulonodular infiltrates on CT scan. The past medical history is remarkable for nodal large B cell lymphoma (CD20/30 +) with extensive bone marrow involvement two years earlier.

The patient had been receiving chlorambucil for several months before her current presentation. A surgical lung biopsy was performed.
Diagnosis
Category 3: Recurrent disease

Recurrent large B cell lymphoma

The spectrum of subsequent disease
- Infection
- Therapy-related lung disease
- Recurrence of original disease
- **Graft versus host disease**
- Post immunosuppression immunoproliferative disease
- Transplant rejection
A 43 year old man presented with progressive shortness of breath and radiologic changes suggesting pulmonary fibrosis.

The past medical history is remarkable for CML diagnosed 7 years earlier and treated with allogeneic bone marrow transplantation from a living related donor.

The intervening years were punctuated by CNS toxoplasmosis and graft-versus-host disease (skin and GI tract). The FEV1 on admission was 46%. The patient also complained of decreased exercise tolerance and unintentional weight loss.

A surgical lung biopsy was performed.
Diagnosis
Category 4: GVHD

Pulmonary graft versus host disease

Pulmonary Graft versus Host Disease

CT findings (> 100 days post transplant)

1. Patchy consolidation and ground glass attenuation
2. Bronchial dilatation
3. Mosaic air-trapping

Spectrum of Pathologic Manifestations
1. Idiopathic pneumonia syndrome (IPS)/ LIP
2. Lymphocytic bronchiolitis
3. Perivascular lymphocyte cuffing (mature T cells)
4. Pulmonary cytolytic thrombi
5. Bronchiolitis obliterans (constrictive bronchiolitis)
6. Advanced pulmonary fibrosis
The spectrum of subsequent disease

- Infection
- Therapy-related lung disease
- Recurrence of original disease
- Graft versus host disease
- Post immunosuppression immunoproliferative disease
- Transplant rejection

A 59 year old man presented with shortness of breath and fatigue. He was 1 month status post his second allogeneic bone marrow transplant for recurrent multiple myeloma. Two weeks prior to admission, a nasal swab was positive for RSV.

Chest imaging initially revealed a slightly nodular peripheral infiltrate and this progressed over the subsequent three weeks to involve predominately mid and lower lung zones bilaterally, with minimal upper lobe infiltrates.

He was treated with aerosolized ribaviran, but his infiltrates progressed.

A surgical lung biopsy was performed.
Diagnosis

Category 5 PILPD/PTLPD

Epstein-Barr virus-associated post-transplant polyclonal lymphoproliferative disorder (EBV-PTLD).

A component of GVHD is present and there are extensive airway reparative changes (squamous metaplasia). No RSV viropathic changes seen.

Multiple pulmonary nodules caused by B-cell post-transplant lymphoproliferative disorder after bone marrow transplantation: monitoring Epstein-Barr virus viral load.


The 5 Take Home Lessons

1. Infection
2. Therapy-related lung disease
3. Recurrence of original disease
4. Post immunosuppression immunoproliferative disease
5. Graft versus host disease
1. Ischemia Reperfusion Injury (I/R; ARDS/DAD): Usually diagnosed on clinical grounds with histologic confirmation with TBBx. The ISHLT severity scoring system is universally used. Rx: High dose steroids which is effective in the vast majority.


3. Humoral Allograft Rejection: Presentation not dissimilar to the above problems and potentially progressing to ARDS. Medical Management: Beyond the First Year (generally listed from most to least common)

- Infections
- Surveillance
- Possible Major Lung Complications
- Medical Management: The Lung Transplant Clinical “Protocol” Presentation usually patchy infiltrates, often bilateral accompanied by fever, leukocytosis and cough. Diagnosis by sputum/bronchoscopy culture. Acute Vascular Allograft Rejection: Related to reactivation EBV infection. Present with lung nodule(s). Dx: EBV viral load by PCR but pathology (FNA, core or VATS biopsy) is the gold standard. Chemotherapy is not indicated for early PTLD. EBV viral load drops before tumor regression by scans.

Possible Major Lung Complications

1. Infections
   - Acute Vascular Allograft Rejection: Often chest xray silent. Symptoms range from none to dyspnea and hypoxemia. Pathology is nonspecific (DAD). Related to reactivation EBV infection. Present with lung nodule(s). Dx: EBV viral load by PCR but pathology (FNA, core or VATS biopsy) is the gold standard. Chemotherapy is not indicated for early PTLD. EBV viral load drops before tumor regression by scans.
   - Humoral Allograft Rejection: Less common as time goes by but not unheard of. Related to EBV or opportunistic infections. Pathology is nonspecific (DAD). Related to reactivation EBV infection. Present with lung nodule(s). Dx: EBV viral load by PCR but pathology (FNA, core or VATS biopsy) is the gold standard. Chemotherapy is not indicated for early PTLD. EBV viral load drops before tumor regression by scans.

Surgical Management: Beyond the First Year (generally listed from most to least common)

- Infections
- Surveillance
- Possible Major Lung Complications
- Medical Management: The Lung Transplant Clinical “Protocol”