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
Lung Disease Timetable Post BMT

- **CHF**
- **DAH/ARDS**
- **Bacterial**
- **Fungal**
- **HS**
- **Post-transplant lymphoproliferative disease**
- **Acute GVHD**
- **Chronic GVHD**
- **Pneumocystis**
- **CMV**
- **Idiopathic interstitial pneumonia**
- **Neutropenic phase**
- **Bacterial (sinopulmonary)**
- **Obstructive airways disease / BO**
- **Restrictive ventilatory defect**

- **Soubani et al, Chest 1996 109:1066-1077**

0 1 2 3 4 5 6… 12 Months after transplantation
The spectrum of subsequent disease

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

### Infection Timetable Post-transplantation

<table>
<thead>
<tr>
<th>Nosocomial</th>
<th>Opportunistic</th>
<th>Comm. Acquired or Persistent</th>
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</thead>
<tbody>
<tr>
<td><strong>Bacterial/ mycobacterial</strong></td>
<td>Wound infections, catheter-related infections, pneumonia</td>
<td>CMV retinitis or colitis</td>
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<tr>
<td>Nocardia</td>
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<td>Papillomavirus, PTLD</td>
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<td>Listeria, tuberculosis</td>
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<td><strong>Fungal</strong></td>
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<td>Candida</td>
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<td>Pneumocystis</td>
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<td>Aspergillus</td>
<td>Endemic fungi</td>
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<td>Cryptococcus</td>
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<td><strong>Viral</strong></td>
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<td>HSV</td>
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<tr>
<td>Hepatitis B and C</td>
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<td></td>
<td>CMV</td>
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<tr>
<td></td>
<td>EBV, VZV, influenza, RSV, adenovirus</td>
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<tr>
<td><strong>Parasitic</strong></td>
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<td>Leishmenia</td>
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<td>Toxoplasma</td>
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<td>Trypanosomes</td>
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<tr>
<td>Strongyloides</td>
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</tbody>
</table>

0 1 2 3 4 5 6 Months after transplantation

Fishman and Rubin, NEJM, 1998; 338:1741-51
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 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 azythromycin and bronchodilators without improvement.

A surgical lung biopsy was performed.
Case 2:
Case 2:
Case 2:
Case 2:
Case 2:
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
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- 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 weightloss.

A surgical lung biopsy was performed.
Diagnosis

Category 4: GVHD

Pulmonary graft versus host disease
Pulmonary Graft versus Host Disease

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
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
The spectrum of subsequent disease

- Infection
- Therapy-related lung disease
- Recurrence of original disease
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- 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 ribavirin, 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 viroplastic 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