CELLULAR AND CHRONIC REJECTION

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Aspen 2014
Kidney, heart, lung, liver, small bowel, pancreas
Pediatric solid organ transplantation

10-year survivals

- Kidney: 92% (7 year survival)
- Heart: 58%
- Lung: 33%
- Liver: 67%
- Small Bowel: 35%
Kidney transplant
T-CELL MEDIATED REJECTION

Pathologic Key Features

- Tubulitis (>5 lymphocytes per tubular cross section) in well-preserved tubules AND inflammation involving more than 25% of the parenchyma, excluding areas of tubulointerstitial scarring (type I rejection)

- Intimal arteritis (type II) or transmural arteritis or fibrinoid necrosis of arteries (type III rejection)

- The presence of either #1 (type I) or #2 (type II or III) is sufficient to diagnose acute T-cell mediated rejection. Both may be but are not necessarily present
Type 1A acute rejection, T-cell mediated
Type IIB acute rejection, T-cell mediated?
Chronic type II rejection
Type III rejection
Pitfalls: T-CELL MEDIATED REJECTION

• Avoid assessing areas with marked interstitial fibrosis and tubular atrophy.

• Assess tubulitis in tubules with at most minimal atrophy.

• Have a low threshold for performing an SV40 immunostain.

• Acute rejection can occur simultaneously with other injuries, such as viral infections.
ACR and T-regs

- Role of NK-T cells?
POLYOMAVIRUS NEPHROPATHY

Pathologic Key Features

• Intranuclear ground-glass inclusions or enlarged nuclei: not always present

• Interstitial inflammation with tubulitis: medulla > cortex

• Positive SV40 IHC in tubular epithelial cell nuclei

• Tubular basement membrane immune complex deposition: subset of cases
POLYOMAVIRUS NEPHROPATHY

Differential Diagnosis

• Acute rejection (type I), borderline changes

• Adenovirus tubulointerstitial nephritis

• Drug-induced acute interstitial nephritis

• Post-transplant lymphoproliferative disorder, plasma cell hyperplasia
POLYOMAVIRUS NEPHROPATHY

Pitfalls

• Viral cytopathic changes often not present

• Have a low threshold for ordering SV40 immunostain

• Carefully evaluate SV40 immunostain for focal nuclear staining

• Concomitant acute rejection can occur with PVN
HEART TRANSPLANTATION
# Acute cellular rejection (heart)

<table>
<thead>
<tr>
<th>Description</th>
<th>1990 grade</th>
<th>2005 grade</th>
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<tbody>
<tr>
<td>Focal mild, mild and focal moderate</td>
<td>1A, 1B, 2</td>
<td>1R</td>
</tr>
<tr>
<td>Multifocal moderate</td>
<td>3A</td>
<td>2R</td>
</tr>
<tr>
<td>Diffuse moderate, severe</td>
<td>3B, 4</td>
<td>3R</td>
</tr>
</tbody>
</table>
First post-transplant bx
Focal mild rejection
Grade 1A (1R)
Mild rejection
Grade 1B (1R)
Multifocal moderate Grade 3A (2R)
Chronic rejection
LUNG TRANSPLANTATION
1996 Working formulation for classification and grading of pulmonary allograft rejection

A. Acute rejection
Grade 0 - None
Grade 1 - Minimal
Grade 2 - Mild
Grade 3 - Moderate
Grade 4 - Severe

B. Airway inflammation - lymphocytic bronchitis/bronchiolitis
Grade 0 - None
Grade 1 - Minimal
Grade 2 - Mild
Grade 3 - Moderate
Grade 4 - Severe
2007 classification and grading of pulmonary allograft rejection

A. Acute rejection

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
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B. Airway inflammation - lymphocytic bronchitis/bronchiolitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>None</td>
</tr>
<tr>
<td>Grade 1(R)</td>
<td>Minimal/Mild</td>
</tr>
<tr>
<td>Grade 2(R)</td>
<td>Moderate/Severe</td>
</tr>
</tbody>
</table>
Minimal airway rejection
Grade 1 (1R)
Mild airway rejection
Grade 2 (1R)
Mild airway rejection
Grade 2 (1R)
Chronic rejection: lung

A

B
LIVER TRANSPLANTATION
Acute cellular rejection
Central and portal vein endothelialitis
ACUTE CELLULAR REJECTION LIVER

Key Features

- Portal and/or central involvement
- Portal mixed infiltrate with lymphocytes, activated lymphocytes, plasma cells, and eosinophils
- Bile ductular damage with cytoplasmic vacuolation and intraepithelial lymphocytes with epithelia cell apoptosis
- Pericentral extravasation of erythrocytes and lymphocytic infiltrate
- Central vein endothelialitis and portal vein branches endothelialitis
- Lobular infiltrates minimal although rare hepatitic pattern possible
- No viral cause evident
## Banff classification for acute cellular rejection

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
</table>
| Indeterminate  | Rare portal areas with infiltrate; Infiltrate not typical of ACR infiltrate  
No endothelialitis |
| Mild           | Some portal areas involved by mixed infiltrate                            
Portal venous radicals with endothelialitis  
No central perivenulitis |
| Moderate       | Most portal areas expanded by rejection type                              |
| infiltrate     | Most/all portal areas with extensive infiltrates AND Central perivenulitis in few/many lobules  
Pericentral hepatocytes dropout  
Portal infiltrates extending into lobules with hepatocyte damage |
Acute ischemic/reperfusion injury

Acute pericholangitis and ductular proliferation
Biliary complications
Adenovirus
EBV hepatitis
PITFALLS: LIVER ACUTE CELLULAR REJECTION

- Neutrophils are not a prominent component of portal infiltrates; if present, think biliary

- Monotonous lymphocytic infiltrate favors viral cause, do Epstein-Barr encoded RNAs (EBER) ISH

- Isolated central venulitis may be the early manifestation in pediatric patients without the portal infiltrates

- A hepatitic pattern always warrants exclusions of other common causes before diagnosing hepatitic pattern of ACR

- Presence of large numbers of plasma cells in infiltrate should warrant exclusion of autoimmune or EBV-related disease

- Central venular endothelialitis and extravasation may be a manifestation of autoimmune hepatitis or EBV hepatitis
Chronic rejection
SMALL BOWEL: AMR
SMALL BOWEL: ACR
SMALL BOWEL: ACR, SEVERE
SMALL BOWEL: CHRONIC REJECTION

A

B

C
Pancreatic transplantation

- Acute cellular rejection
  - Mild (grade I)
  - Moderate (grade II)
  - Severe (grade III)
Pancreatic transplantation

- Chronic rejection/graft sclerosis
  - T-cell mediated
  - Antibody mediated
  - Stimulation of fibrosis
  - Grades I-III
Pancreatic transplantation

- Antibody-mediated rejection
  - Hyperacute rejection
  - Acute AMR
  - Chronic AMR
SUMMARY

- Acute rejection is T-cell mediated
- Mostly treatable and less severe now

- Chronic rejection is fibrosis of epithelial lined tubes and arteries
- Main cause for long term morbidity and mortality