Histological Assessment of Late Biopsies from the Liver Allograft

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Histological findings in 1108 biopsies obtained > 1 year post-transplant, Liver Unit, QE Hospital, Birmingham

<table>
<thead>
<tr>
<th>Main Diagnosis</th>
<th>Number (%) Of Cases</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal / near normal</td>
<td>169 (15)</td>
<td></td>
</tr>
<tr>
<td>Rejection</td>
<td>55 (5)</td>
<td>Many cases co-exist with other patterns of graft damage</td>
</tr>
<tr>
<td>Biliary obstruction / cholestasis</td>
<td>22 (2)</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>402 (36)</td>
<td>94 (23%) cases related to recurrent disease 308 (77%) cases other/unknown cause</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>194 (18)</td>
<td></td>
</tr>
<tr>
<td>Other findings</td>
<td>266 (24)</td>
<td>Fatty change, vascular/structural changes, fibrosis</td>
</tr>
</tbody>
</table>

Data from Liver Unit Database, Jan 2002 – Jan 2007

Reason for biopsy - 822 (74%) protocol, 286 (26%) clinically indicated

Many cases have more than one pattern of damage
Main Pathological Changes in Biopsies >12 Months Post-transplant

- **Rejection**
  - Less common than in early post-transplant period
  - May have different histological features

- **Recurrent disease**
  - General issues
  - Assessment of biopsies from HCV-positive individuals

- **De novo disease**
  - General issues
  - De novo autoimmune hepatitis

- **Other findings in late biopsies**
  - “Idiopathic” chronic hepatitis
  - Vascular/structural abnormalities
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Acute Cellular Rejection – Typical Histological Features

- Portal inflammation (mixed population)
- Bile duct inflammation
- Venous endothelial inflammation
Late Cellular Rejection
Different Histological Features

• Portal inflammation predominantly mononuclear
• Inflammation of bile ducts and venular endothelium less conspicuous
• More prominent interface hepatitis
• More prominent lobular hepatitis
• Overall features resemble those seen in chronic hepatitis
  (e.g. viral or autoimmune)

• More recent studies suggest that zone 3 necroinflammatory lesions
  (“central perivenulitis”) may also be a feature of late cellular rejection
  (Banff Working Party, Hepatology 2006; 44: 489-501)
• Central perivenulitis may occur as an isolated lesion (without typical
  portal rejection changes)
Liver Allograft Rejection - “Central Perivenulitis”

Liver biopsy, 6 months post-transplant. Worsening LFTs (AST 2xN)

**Other possible causes of zone 3 necroinflammation**

Autoimmune hepatitis
- recurrent AIH
- de novo AIH

Viral hepatitis (recurrent or acquired)
- HBV
- HCV
Central Perivenulitis in Liver Allograft Rejection

Clinico-pathological Features
• Present later than cases with pure portal rejection
• Often associated with raised transaminase levels
• Less responsive to immunosuppression
• More likely to progress to chronic rejection

Clinical Significance
• Transitional phase between acute (reversible) rejection and chronic (irreversible) rejection
• Precedes bile duct loss
• Early recognition and prompt treatment can prevent progression to chronic rejection (graft failure due to chronic rejection now < 2%)
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# Disease Recurrence in the Liver Allograft

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>&lt; 10% (up to 85% in earlier studies)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>PBC</td>
<td>30-40%</td>
</tr>
<tr>
<td>PSC</td>
<td>20-30%</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>20-30%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10 - 30%</td>
</tr>
<tr>
<td>NASH (&quot;cryptogenic&quot; cirrhosis)</td>
<td>20-40%</td>
</tr>
</tbody>
</table>

Recurrent disease = commonest cause of late graft dysfunction
Disease Recurrence in Liver Allografts - Diagnostic Problems

(1) Recurrent disease and other transplant complications

(A) **Histological Similarities**
- Hepatitis C v Acute rejection
- PBC/PSC v Chronic rejection
- PSC v Ischaemic biliary complications

(B) **Other Interactions**
- Higher incidence of rejection (acute and chronic) in:
  - patients transplanted for autoimmune liver disease
  - recurrent HCV

- Changes seen in late biopsies often reflect more than one pathological process
- Clinical picture often complex
- Histology may help to identify the dominant cause of graft damage
Disease Recurrence in Liver Allografts - Diagnostic Problems

(2) Effects of immunosuppression

LESS aggressive disease - immune-mediated disease (e.g. AIH, PBC)

MORE aggressive disease - viral hepatitis (e.g. HBV, HCV)

(atypical patterns)
Hepatitis C in the Liver Allograft

- HCV cirrhosis commonest indication for liver transplantation
- Re-infection is universal (occurs within a few hours)
- Most cases (>80%) develop graft inflammation
- Many progress to cirrhosis
  - 20% by 5 years, up to 50% at 10 years
- Reduced graft and patient survival
Hepatitis C in the Liver Allograft
Differences Compared with HCV in the Native Liver

• More aggressive disease
  – More severe inflammatory activity (more rapid progression to fibrosis and cirrhosis)
  – Cholestatic features (fibrosing cholestatic hepatitis)

• Hepatitis C and rejection
Recurrent Hepatitis C
prominent lobular inflammation with zone 3 necrosis

- Are these changes related to HCV alone?
- or HCV + another graft complication
  - rejection with central perivenulitis
  - de novo AIH
Aggressive Recurrent HCV

- Male, age 52. 21 months post-LT for HCV
- Antiviral therapy recently stopped because of nephric abscess
- Presented with acutely deranged LFTs (AST 650)
- Became HCV-RNA positive
HEPATITIS C
VERSUS
CELLULAR REJECTION
Hepatitis C versus Cellular Rejection - Portal Inflammatory Lesions

Hepatitis C

Rejection
HEPATITIS C

VERSUS

AND

CELLULAR REJECTION
Recurrent Hepatitis C and Acute Rejection

- Recognition that AR and recurrent HCV overlap in time and histological features

- Prospective study of biopsies from 48 HCV positive patients
  - Identify main cause of graft damage
  - Verify diagnosis by subsequent clinical course

- In most cases where dual pathology suspected rejection changes are mild
  - HCV best considered as the primary diagnosis
  - No additional immunosuppression required

- Increased immunosuppression should be considered as a treatment option if rejection changes moderate or severe
Main Pathological Changes in Biopsies >12 Months Post-transplant

• Rejection
  – Less common than in early post-transplant period
  – May have different histological features

• Recurrent disease
  – General issues
  – Assessment of biopsies from HCV-positive individuals

• De novo disease
  – General issues
  – De novo autoimmune hepatitis

• Other findings in late biopsies
  – “Idiopathic” chronic hepatitis
  – Vascular/structural abnormalities
## De Novo Disease in the Liver Allograft

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DE NOVO OCCURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>YES</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>YES</td>
</tr>
<tr>
<td>PBC</td>
<td>NO</td>
</tr>
<tr>
<td>PSC</td>
<td>NO (but ischaemic cholangitis resembles PSC)</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>YES</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Possible</td>
</tr>
<tr>
<td>NASH</td>
<td>YES</td>
</tr>
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</table>
‘De Novo’ Autoimmune Hepatitis in the Liver Allograft


1. Classical biochemical, serological and histological features of AIH may develop in patients transplanted for other diseases

2. Higher prevalence in paediatric population (5-10%), compared with adults (1-2%)
   - Immunosuppressive drugs interfering with normal T cell maturation

3. Most cases respond to increased immunosuppression. Occasional cases have progressed to graft failure

4. Areas of overlap between de novo AIH and rejection
   - antibodies to graft antigens may indicate an alloimmune response
   - de novo AIH could represent a form of late cellular rejection
Chronic Hepatitis in the Liver Allograft
Features favouring an autoimmune aetiology

- Portal inflammation with numerous plasma cells
- Prominent interface hepatitis
- Lobular inflammation (plasma cell rich) with zone 3 necrosis
- Lobular changes in de novo AIH more prominent than in AIH in the native liver (Salcedo 2002, Aguilera 2004)
Pegylated Interferon Therapy for HCV and De Novo AIH

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
</tr>
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<tbody>
<tr>
<td>Chlongitas</td>
<td>1</td>
</tr>
<tr>
<td>Transplantation 2006;81:488-90.</td>
<td></td>
</tr>
<tr>
<td>Kontorinis</td>
<td>1</td>
</tr>
<tr>
<td>Berardi</td>
<td>9/44 patients</td>
</tr>
</tbody>
</table>

- All 11 cases had biochemical, serological and histological features compatible with AIH
- 9/11 were HCV-RNA negative
- 7/11 responded to treatment with immunosuppression
Patterns of recurrent hepatitis C after liver transplantation
(Khettry Human Pathol 2007; 38: 443-452)

- 61 cases of recurrent HCV
  - 52 “typical” recurrent HCV
  - 9 “AIH-like”

- Histological Findings in “AIH-like” HCV
  - Plasma cell-rich infiltrate (portal and/or lobular)
  - Higher frequency of central perivenulitis (5/9 vs 8/52 typical HCV)
  - More rapid fibrosis progression

- Other Findings in “AIH-like” HCV
  - Increased serum immunoglobulins and/or autoantibodies (6/8 cases)
Main Pathological Changes in Biopsies >12 Months Post-transplant

• Rejection
  – Less common than in early post-transplant period
  – May have different histological features

• Recurrent disease
  – General issues
  – Assessment of biopsies from HCV-positive individuals

• De novo disease
  – General issues
  – De novo autoimmune hepatitis

• Other findings in late biopsies
  – “Idiopathic” chronic hepatitis
    • Commonest histological diagnosis in late post-transplant biopsies
    • In cases where viral and autoimmune causes have been excluded, could this be a form of rejection?
Chronic Hepatitis in the Liver Allograft
Portal Inflammatory Changes
Chronic Hepatitis in the Liver Allograft
Lobular Inflammatory Changes
Chronic Hepatitis in Late Post-Transplant Biopsies
Could this be a form of late cellular rejection?

• In the adult population, excluding recurrent disease as a cause for chronic hepatitis is difficult
  – Most of the diseases for which transplantation carried out in adults have the potential to recur, with features of chronic hepatitis
  – Histological features of “non-specific” chronic hepatitis may precede other diagnostic abnormalities of recurrent disease (AIH and PBC)

• Alternative Approaches
  – Paediatric patients
  – Adults transplanted for non-recurring diseases
Progressive histological damage following paediatric liver transplantation
Evans HM, Kelly DA, McKiernan PJ, Hübscher SG Hepatology 2006; 43: 1109-1117

• 158 patients followed for > 5 years post-transplant
• Only 8 transplanted for diseases known to recur
  – 5 primary sclerosing cholangitis
  – 3 autoimmune hepatitis
• Protocol biopsies at 1, 5 and 10 years
Progressive histological damage following paediatric liver transplantation
Evans HM, Kelly DA, McKiernan PJ, Hübscher SG Hepatology 2006; 43: 1109-1117

<table>
<thead>
<tr>
<th>Histological Diagnosis</th>
<th>1 year (n=113)</th>
<th>5 years (n=135)</th>
<th>10 years (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/ near normal</td>
<td>68.2%</td>
<td>45.2%</td>
<td>31.3%</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>22.1%</td>
<td>43.0%</td>
<td>64.0%</td>
</tr>
<tr>
<td>Rejection (acute or chronic)</td>
<td>2.7%</td>
<td>2.2%</td>
<td>0</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>6.2%</td>
<td>7.4%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Recurrent Disease</td>
<td>0.9%</td>
<td>0.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
Chronic Hepatitis - Severity of Fibrosis at Different Times

Mild

Moderate

Severe

Time post-OLT

1 year 5 years 10 years

none mild (fibrous portal expansion) moderate (bridging fibrosis) severe (cirrhosis)
Further findings in chronic hepatitis cases

- 70-80% associated with auto-antibodies, many in high titre
  (vs 10-13% in cases with normal histology, all in low titre – ANA ≤ 1 in 40)

- Only 6% fulfil other diagnostic criteria for de novo autoimmune hepatitis
  - Median AST levels < 2xN
Natural history of unexplained chronic hepatitis following liver transplantation

  - Alcoholic liver disease, with no significant alcohol consumption post-LT (n=201)
  - Drug-induced acute liver failure (n=87)

- 46/143 (32%) patients biopsied > 6 months had chronic hepatitis
  - Median time of diagnosis 15 months (6-72)
Natural history of unexplained chronic hepatitis following liver transplantation


Follow-up

• 30/46 patients with chronic hepatitis had one or more subsequent biopsies
  – median time from index to latest biopsy 3.9 years (range 0.6-9.4)
  – Fibrosis progressed in 13, same in 14, improved in 3

• Factors correlating with fibrosis progression
  – High titre autoantibodies (ANA > 1:1600)
  – Plasma cell rich infiltrate in index biopsy
  – Female donor sex
  – Alkaline phosphatase levels
Chronic Hepatitis with “Autoimmune Features”
Clinical Implications

Graft Monitoring
- routine LFTs unreliable
- protocol biopsies
- autoantibody testing

Treatment (immunosuppression to prevent disease progression?)
- criteria for treatment
- monitoring therapeutic responses
- patients transplanted for hepatitis C

Many patients have mild changes with no evidence of fibrosis
- Does mild (non-progressive) portal hepatitis represent a form of graft tolerance?
- Can liver biopsy help to identify patients in whom immunosuppression can be reduced or withdrawn?
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Nodular Regenerative Hyperplasia
Male age 46 – protocol biopsy 12 months post-transplant for Wilson’s disease
Perisinusoidal Fibrosis
Nodular changes in late post-transplant biopsies  

- Frequency  
  2% - 82%

- Possible Causes (impaired sinusoidal blood flow)  
  - Vascular problems (portal/hepatic venous insufficiency)  
  - Drug toxicity (azathioprine)  
  - Immune mediated (rejection related damage to sinusoidal/vascular sinusoidal endothelium)

- Clinical Consequences  
  - 6/26 cases reported from KCH London required retransplantation  
    (Slapak Hepatology 1997; 25: 195-202)  
  - 7/14 cases from Mayo Clinic symptomatic with features of portal hypertension (ascites - 7, varices - 4)  
    (Devarbhavi Liver Transpl. 2007;13:1552-6.)  
  - Others noted as incidental finding
Liver Biopsy Interpretation for Causes of Late Liver Allograft Dysfunction

Banff Working Group

(Hepatology 2006;44:489-501.)

Idiopathic Posttransplantation Hepatitis?

Obaid S. Shaikh and A. Jake Demetris

Liver Transplantation 13:943-946, 2007

The Significance of Nodular Regenerative Hyperplasia in the Transplanted Liver

Alyssa Krasinskas

Liver Transplantation 13:1496-1497, 2007