Acute Hepatitis
Including Acute Liver Failure

Ahmed Elsharkawy
Liver Unit, Queen Elizabeth Hospital, Birmingham

Stefan Hübscher
Institute of Immunology & Immunotherapy, University of Birmingham
Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham
Case 1
16 year old boy

- Presented to local hospital June 2013
- 2 week history of fatigue, anorexia, nausea and abdominal pain – off school
- Increasing jaundice and pruritus
- Weight loss over the same time period
- No recent foreign travel
- No tattoos, IVDU, paracetamol use, high risk sexual behaviour
- No family history
- PMH of asthma, allergic rhinitis and inguinal hernia repair
Admission Bloods and Liver Screen

- Hb 15, WCC 7.7, Plt 287, MCV 67.8
- Na 137, K 4.1, Ur 4.1, Creat 70
- Bili 197, ALT 1965, ALP 273, Alb 36
- PT 16.3 seconds
- Paracetamol level 5
- Ferritin 1850
- Autoimmune screen negative, immunoglobulins normal, caeruloplasmin normal, Hep A, B C, E negative, CMV serology negative, EBV IgG positive but Monolatex test negative
USS at Local Hospital

- The GB appears contracted
- Liver and CBD are normal with no intrahepatic duct dilatation
- The kidneys, spleen and pancreas are normal
- Vasculature all patent
- No ascites
Progress at Local Hospital

- **Bili**: Blue line
- **ALT**: Green line

Day 0, Day 2, Day 6, Day 8
Days 9 + 10

- Has transjugular liver biopsy performed
- Transferred to QE in Birmingham with biopsy in formalin
- Further history reveals no further aetiological clues
- Patient clinically well but itch becoming increasingly troublesome
Why was the liver biopsy performed?

- Evidence of on-going and worsening inflammatory activity?
- Is this autoimmune hepatitis?
- Is there anything histologically to predict a response to immunomodulatory therapy?
The Biopsy
Liver Biopsy in Acute Hepatitis
Histological Approach

1. Is this acute or chronic damage?

2. How severe is the damage?

3. What is the cause?
Case 1 - Histological Findings

• **Portal inflammation**
  – Mixed population (lymphocytes, neutrophils, eosinophils)

• **Bile ductular reaction**

• **Generalised spotty lobular inflammation, associated with:**
  – Acidophil body formation
  – Lobular disarray
  – Small foci of confluent necrosis, one focus of bridging necrosis
Case 1 - Diagnosis

• Acute hepatitis
• Moderately severe inflammatory activity, including foci of confluent/bridging necrosis
• No strong aetiological pointers
  – Consider viral agents, drugs and autoimmune hepatitis in differential diagnosis
Days 11 - 16

- Biopsy report received
- Started on prednisolone 40 mg od on day
- LFTs started to improve (see next slide)
- Discharged with weekly outpatient follow up – no ascites at the time
- Did well on 20 mg of prednisolone
- Only thing positive in repeat liver screen is a weakly positive ASMA
- Now discharged from our follow up
Prednisolone
Started
Final Diagnosis

Steroid Responsive Seronegative Hepatitis
Steroid Responsive SNH

- Poorly understood entity
- Rare
- May represent ‘seronegative’ autoimmune hepatitis
- Limited ability to predict response to steroids – presence of ascites may be important
- No data on use of second line agents such as azathioprine
- Limited data on relapse rates
Case 2
16 Year Old Girl

- Referred from GP in December 2012 with a peripheral WCC of 333
- No other PMH
- Nilotinib (second generation tyrosine kinase inhibitor) started on 24.12.2012
- LFTs prior to starting treatment normal
- Good cellular and cytogenetic response almost immediately
Changes in Blood Tests Over Time

- ALT
- Bili
- ALP
- WCC

Dates:
- 21/12/2012
- 21/01/2013
- 21/02/2013
- 21/03/2013
- 21/04/2013
- 21/05/2013
- 21/06/2013
- 21/07/2013
- 21/08/2013
- 21/09/2013
- 21/10/2013
- 21/11/2013
- 21/12/2013
Seen in Liver Clinic Jan 2014

- Feeling well
- No symptoms attributable to liver disease
- No FH of liver disease
- Fibroscan elevated at 10.0 Kpa
- Literature search performed – no reports of nilotinib induced liver toxicity
- Full liver screen sent
Liver Screen

- Hep A,B,C negative
- Immunoglobulins normal
- Extended autoantibody screen negative
- HEV RNA PCR negative
- CMV PCR negative
- EBV PCR negative
- A1AT, copper studies normal
- Ferritin low (16)
Why was the liver biopsy performed?

• To provide confirmatory evidence for the clinical diagnosis of a nilotinib induced drug injury given the absence of previous reports of this in the literature

• To assess the degree of inflammation and fibrosis
The Biopsy
Case 1 - Histological Findings

- **Lobular Inflammation**
  - Mainly centrilobular
  - Mild bilirubinostasis
  - No evidence of confluent or bridging necrosis

- **Moderate fibrosis**
  - Mainly centrilobular with perisinusoidal pattern
  - Occasional foci of early bridging
  - Connective tissue stains suggest fairly recent (collagen fibres present without elastic fibres)

- **Focal (mild) portal tract changes**
  - Mild inflammation and ductular reaction
Case 1 - Diagnosis

• Lobular hepatitis
  – Clinical circumstances (and centrilobular distribution of inflammatory changes) favour drug reaction as most likely diagnosis

• Foci of fibrosis and bridging may reflect previous episodes of centrilobular injury
Drug-induced Acute Hepatitis

- Drugs account for approximately 10% of cases of acute hepatitis and acute liver failure (Ramachandran & Kakar 2009, Reuben 2010)
- Many agents implicated – antimicrobial drugs commonest

Histological features

- Frequently indistinguishable from other causes of acute hepatitis (e.g. viral hepatitis, autoimmune hepatitis)
- Features favouring a drug aetiology:
  - Predominantly centrilobular (zone 3) inflammation
  - Disproportionately severe / well-circumscribed necrosis (relatively little inflammation – lobular and/or portal)
  - Unusual patterns of necrosis - e.g periportal (zone 1) necrosis
  - Unusually prominent cholestasis
  - Eosinophils, granulomas
SEARCH THE LIVERTOX DATABASE

Search for a specific medication, herbal or supplement:

Browse by first letter of medication, herbal or supplement:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

LIVERTOX® provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements. LIVERTOX also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LIVERTOX website provides a comprehensive resource for physicians, researchers, and the public.
OVERVIEW

Nilotinib

Introduction
Nilotinib is a selective tyrosine kinase receptor inhibitor used in the therapy of chronic myelogenous leukemia. Nilotinib therapy is associated with transient elevations in serum aminotransferase levels and rare instances of clinically apparent acute liver injury.

Background
Hepatotoxicity

Elevations in serum aminotransferase levels are common during nilotinib therapy, occurring in up to 70% of patients, but rising to greater than 5 times the upper limit of normal (ULN) in only 4% to 9% of recipients. These abnormalities are usually asymptomatic. If levels are markedly elevated (ALT or AST persistently greater than 5 times ULN or bilirubin more than 3 times ULN), dose adjustment or temporary discontinuation and restarting at a lower dose is recommended. In high doses, nilotinib is also associated with elevations in serum bilirubin, but these are largely in the indirect (unconjugated) fraction and are not associated with serum enzyme elevations or symptoms, resolving with dose adjustment or discontinuation. The majority of patients with marked bilirubin elevations on nilotinib therapy have underlying Gilbert Syndrome. There have been no published case reports of clinically apparent liver injury attributed to nilotinib, but it has been used in a restricted population of patients for a relatively short period of time. The product label does mention hepatitis and jaundice as reported adverse events. Severe tumor lysis syndrome with multiorgan including hepatic failure can occur with nilotinib but is rare. In addition, most other tyrosine kinase receptor inhibitors have been linked to rare instances of clinically apparent liver injury, usually arising after 1 to 8 weeks of treatment and presenting with a hepatocellular or mixed pattern of serum enzyme elevations. Immunoallergic and autoimmune features are uncommon. The liver injury can be severe and lead to acute liver failure. Routine monthly monitoring of liver tests during therapy with tyrosine kinase receptor inhibitors is recommended.

Mechanism of Injury

The cause of the liver injury due to nilotinib is unknown. Nilotinib is metabolized in the liver largely by the cytochrome P450 system, and liver injury may be due to accumulation of a toxic intermediate or from a drug-drug interaction with other medications.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose reduction or temporary cessation. Cross reactivity of the hepatic injury with other tyrosine kinase inhibitors is not common but can occur. In using this medication, monitoring of transaminase levels should be performed on a regular basis.
Changes After Switch to Imatinib

- ALT
- Bili
- ALP
- WCC
Clinical Progress

• Well
• LFTs normalised
• CML remains in remission
• 1.5 years later LFTs remain perfectly normal
• Her fibroscan readings fell from 10.0 KPa to 6.4 KPa and finally 5.3 KPa over a period of 14 months
Case 3
38 year old lady

- Had been unwell with gastroenteritis 2 months prior to admission after holiday in Ireland
- 1 month after that started on fluoxetine
- 2 days later noticed that she was jaundiced
- Was admitted at that stage and then discharged
- Readmitted with worsening jaundice, peripheral oedema and ascites
- PMH of asthma and fibroids
- Alcohol – half a bottle of wine five days a week for last 2 years
Admission Bloods and Liver Screen

- Hb 13.8, WCC 7.6, MCV 91.4, plts 195
- INR 1.8
- ALT 585, Bili 261, ALP 279, GGT 273, Alb 34, Na 135, K 4.1, Ur 2.7, Creat 56
- Hepatitis A, B, C and E negative
- Autoimmune profile and immunoglobulins negative
- Other liver screen all negative
- Leptospirosis negative
• Patchy enhancement in the liver but no focal lesions
• Portal vein and hepatic vein patent
• Normal CBD
• Rest of organs normal
• No ascites
Progress Days 1 - 8

- Liaised daily with QE
- Started on prednisolone on day 1
- No significant change in LFTs
- Prednisolone stopped day 8
- Transferred to QE in view of on-going coagulopathy and jaundice
- No suggestion of hepatic encephalopathy
Day 9 Admission to QE

- Bilirubin 236
- ALT 225
- Albumin 25
- INR 2.6
- USS – fatty infiltration of the liver
- Small amount of ascites seen
- No liver flap
Days 10 - 14

- In status quo
- No sign of hepatic encephalopathy – number connection tests all less than 30 seconds
- History reviewed fully on multi-consultant ward round
- Some concerns about alcohol intake although no suggestion of dependency clinically
- Also AST (250) higher than ALT (150 at this stage)
- Caeruloplasmin low – ? Wilson’s
- Transjugular liver biopsy arranged
Biopsy Planned

• Questions –
  1. Is there evidence of acute alcoholic hepatitis
  2. Is there any suggestion of Wilson’s disease
  3. How severe is the amount of necrosis in the liver
  4. Is there any suggestion of spontaneous recovery
Case 3

Liver Biopsy
Liver Biopsy – Case 3

Histological Findings

• Recent panacinar necrosis
  – Moderate inflammation (including ceroid laden macrophages ++)
  – Periportal ductular reaction
  – One small nodule surviving hepatocytes

Comment

• Likely to be a manifestation of severe acute hepatitis
• No obvious aetiological pointers
• No features to suggest alcoholic hepatitis or Wilson disease
Days 14 - 20

- Stable
- Biopsy suggests unlikely to recover
- Transplant assessment tests performed
- On day 18 develops liver flap in association with INR of 3.9
- Sodium at the time 119
- Transferred to ITU for CVVH
- Listed for super-urgent liver transplant on day 19 once sodium above 125
- Transplant done on day 20
Transplant
Graph of ALB, INR Test Results

Transplant
Case 3

Hepatectomy Specimen
Case 3. Macroscopic Appearances
Shrunken liver, weight 640 g. Wrinkled/knobably capsular surface
Case 3 - Macroscopic Appearances
Case 3 - Macroscopic Appearances
Right Lobe
Case 3 - Macroscopic Appearances
Left lobe
Could this be cirrhotic?
Recent Post-Necrotic Collapse versus Longstanding Fibrosis
Use Of Connective Tissue Stains

<table>
<thead>
<tr>
<th>Stain</th>
<th>Material Demonstrated</th>
<th>Distribution In Normal Liver</th>
<th>Changes In Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulin</td>
<td>Type III collagen fibres</td>
<td>Portal tracts, hepatic sinusoids</td>
<td>Collapse of reticulin framework in areas of recent liver cell necrosis. (few days)</td>
</tr>
<tr>
<td>Haematoxylin</td>
<td>Type I collagen fibres</td>
<td>Portal tracts, walls of hepatic veins</td>
<td>Increased in hepatic fibrosis (weeks/months)</td>
</tr>
<tr>
<td>Van Gieson</td>
<td>Elastic fibres</td>
<td>Portal tracts, walls of hepatic veins</td>
<td>Found in long-standing fibrosis/cirrhosis (months/years)</td>
</tr>
</tbody>
</table>
Ceroid Pigment Laden Macrophages

PAS-diastase

CD 68
Rhodanine
Other Changes Seen in Areas of Parenchymal Necrosis

**Congestion**

May suggest a vascular problem – e.g. venous outflow obstruction
Hepatectomy Specimen – Case 3

Histological Findings

- **Large areas of panacinar necrosis (multi-acinar necrosis)**
  - Periportal ductular reaction
  - Inflammation of hepatic veins

- **Surviving areas of liver parenchyma**
  - Nodular regeneration
  - Fatty change
  - Confluent /bridging necrosis
  - Little inflammation
Hepatectomy Specimen – Case 3

Diagnosis

- Severe acute hepatitis with multiacinarn necrosis (submassive hepatic necrosis)
- No strong aetiological pointers ("seronegative hepatitis")
Post Transplant Progress

- Spent 3 days on intensive care
- Spent another 5 days on the ward
- On standard immunosuppresion
- No episodes of rejection
- Doing very well
- 3 years later bloods remain normal
## Most recent bloods

<table>
<thead>
<tr>
<th>Test</th>
<th>04/07/13</th>
<th>15/07/13</th>
<th>29/07/13</th>
<th>13/08/13</th>
<th>09/09/13</th>
<th>10/10/13</th>
<th>05/12/13</th>
<th>11/12/13</th>
<th>06/02/14</th>
<th>22/05/14</th>
<th>17/07/14</th>
<th>16/10/14</th>
<th>15/10/15</th>
<th>04/11/15</th>
<th>16/11/15</th>
<th>22/10/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Transplant</td>
<td>59.3</td>
<td>62.1</td>
<td>61.8</td>
<td>63.6</td>
<td>63.3</td>
<td>63.1</td>
<td>62.4</td>
<td>60.7</td>
<td>59.7</td>
<td>59.9</td>
<td>61.9</td>
<td>61.9</td>
<td>61.9</td>
<td>63.4</td>
<td>63.5</td>
<td>66.9</td>
</tr>
<tr>
<td>BMI</td>
<td>81</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>79</td>
<td>79</td>
<td>83</td>
<td>75</td>
<td>77</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>73</td>
<td>85</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>3.6</td>
<td>4.1</td>
<td>3.8</td>
<td>3.7</td>
<td>3.7</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>53</td>
<td>45</td>
<td>45</td>
<td>51</td>
<td>51</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Urea</td>
<td>53</td>
<td>45</td>
<td>45</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Creat</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>K</td>
<td>4.0</td>
<td>4.2</td>
<td>4.2</td>
<td>4.7</td>
<td>4.5</td>
<td>4.5</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>AST</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>ALT</td>
<td>32</td>
<td>31</td>
<td>25</td>
<td>22</td>
<td>23</td>
<td>23</td>
<td>21</td>
<td>19</td>
<td>16</td>
<td>12</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>BILU</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ALP</td>
<td>113</td>
<td>59</td>
<td>52</td>
<td>35</td>
<td>36</td>
<td>38</td>
<td>39</td>
<td>33</td>
<td>34</td>
<td>31</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>GGT</td>
<td>42</td>
<td>41</td>
<td>43</td>
<td>47</td>
<td>46</td>
<td>41</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>ALB</td>
<td>51.7</td>
<td>5.7</td>
<td>6.0</td>
<td>6.6</td>
<td>6.6</td>
<td>5.3</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>GLUC</td>
<td>5.1</td>
<td>2.42</td>
<td>2.34</td>
<td>2.31</td>
<td>2.42</td>
<td>2.45</td>
<td>2.37</td>
<td>2.36</td>
<td>2.40</td>
<td>2.41</td>
<td>2.33</td>
<td>2.32</td>
<td>2.41</td>
<td>2.36</td>
<td>2.40</td>
<td>2.41</td>
</tr>
<tr>
<td>Hb g/L</td>
<td>116</td>
<td>122</td>
<td>127</td>
<td>133</td>
<td>132</td>
<td>126</td>
<td>107</td>
<td>111</td>
<td>107</td>
<td>119</td>
<td>122</td>
<td>119</td>
<td>122</td>
<td>129</td>
<td>131</td>
<td>131</td>
</tr>
<tr>
<td>CRP</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Albumin/creatinine</td>
<td>140.12</td>
<td>172.82</td>
<td>171.99</td>
<td>156.17</td>
<td>139.07</td>
<td>108.57</td>
<td>116.64</td>
<td>127.61</td>
<td>139.22</td>
<td>159.45</td>
<td>159.45</td>
<td>159.45</td>
<td>159.45</td>
<td>159.45</td>
<td>159.45</td>
<td>159.45</td>
</tr>
<tr>
<td>Creatinine IV</td>
<td>3.7</td>
<td>7.3</td>
<td>5.7</td>
<td>6.5</td>
<td>8.3</td>
<td>5.0</td>
<td>6.4</td>
<td>3.8</td>
<td>5.9</td>
<td>4.2</td>
<td>3.7</td>
<td>6.0</td>
<td>3.9</td>
<td>4.8</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Hydrocortisone IV</td>
<td>532</td>
<td>352</td>
<td>318</td>
<td>263</td>
<td>254</td>
<td>238</td>
<td>247</td>
<td>239</td>
<td>194</td>
<td>203</td>
<td>199</td>
<td>224</td>
<td>275</td>
<td>237</td>
<td>307</td>
<td>307</td>
</tr>
<tr>
<td>Predisone</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tacrolimus (Oral)</td>
<td>4.7</td>
<td>4.6</td>
<td>5.6</td>
<td>6.2</td>
<td>7.3</td>
<td>6.6</td>
<td>5.8</td>
<td>6.5</td>
<td>4.6</td>
<td>7.0</td>
<td>5.4</td>
<td>5.0</td>
<td>11.0</td>
<td>2.9</td>
<td>3.9</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Final Diagnosis

Seronegative hepatitis associated with fulminant liver failure requiring transplantation
Changing Role of Liver Biopsy in Acute Hepatitis

• Many of the classical morphological studies of acute hepatitis were carried out before the main causes had been discovered.

• Most cases of acute hepatitis now diagnosed on the basis of clinical, biochemical and serological findings and liver biopsy is rarely indicated.

• Liver biopsy may still be carried out in cases where the clinical presentation is atypical or the cause is uncertain:
  – Confirm diagnosis of acute hepatitis.
  – Determine disease severity.
  – Identify possible aetiopathological factors (including cases of acute liver injury not related to hepatitis).
Liver Biopsy in Acute Hepatitis
Histological Approach

1. Is this acute or chronic damage?

2. How severe is the damage?

3. What is the cause?
Patterns of Inflammation in the Liver

- **Portal Inflammation**
  - Most chronic liver diseases (e.g. viral, autoimmune)
  - Also seen in acute hepatitis

- **Lobular Inflammation**
  - Main pattern in acute hepatitis
  - Varying degrees of lobular inflammation also commonly present in chronic viral and autoimmune hepatitis

- **Mixed portal and lobular inflammation**

Pattern of inflammation alone cannot reliably distinguish chronic from acute hepatitis

- Clinical context
- Assessment of fibrosis (progressive fibrosis versus post-necrotic collapse)
Severe Acute Hepatitis (e.g. case 3)
Acute versus Chronic Damage – Diagnostic Problems

Clinical

Severe acute hepatitis versus:

• decompensated chronic liver disease (e.g. Wilson disease)
• acute exacerbation of chronic liver disease (e.g. autoimmune hepatitis, hepatitis A/E superimposed on underlying cirrhosis)

Histological

• Areas of bridging necrosis & nodular regeneration can resemble changes occurring in cirrhosis
• Areas of multiacinar necrosis can resemble inflamed fibrous septa in cirrhosis
Multiacinar Necrosis in Severe Acute Hepatitis (e.g. case 3)

Acute versus Chronic Damage - Helpful pointers

- Clinical context
- Identification of normal vascular relationships
- Use of connective tissue stains to determine age of lesions
Liver Biopsy in Acute Hepatitis
Histological Approach

1. Is this acute or chronic damage?

2. How severe is the damage?

3. What is the cause?
Liver Cell Death in Acute Hepatitis

<table>
<thead>
<tr>
<th>Pattern of Cell Death</th>
<th>Histological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotty necrosis</td>
<td>Apoptosis of individual hepatocytes (acidophil bodies)</td>
</tr>
<tr>
<td>Confluent necrosis (zone 3)</td>
<td>Loss of groups of adjacent liver cells</td>
</tr>
<tr>
<td>Bridging necrosis</td>
<td>Confluent necrosis linking vascular structures (central-central or central-portal bridging)</td>
</tr>
<tr>
<td>Panacinar necrosis</td>
<td>Loss of hepatocytes in an entire acinus</td>
</tr>
<tr>
<td>Multiacinar necrosis</td>
<td>Panacinar necrosis involving several adjacent acini</td>
</tr>
</tbody>
</table>

- Apoptosis > necrosis (in mild forms)
- Severe necro-inflammatory lesions uneven in distribution
  - Sampling variability in liver biopsies
  - Extent of hepatocyte necrosis predictive of poor outcome in some studies (Katoonizadeh 2006, Miraglia 2006, Rastogi 2011)
Liver Biopsy in Acute Hepatitis
Histological Approach

1. Is this acute or chronic damage?

2. How severe is the damage?

3. What is the cause?
Acute Hepatitis - Common Causes

1. Viral
   • Hepatitis viruses – A, B, C, D, E
   • Other viruses – e.g. CMV, EBV, HSV

2. Drugs

3. Autoimmune

4. Unknown
   • Seronegative hepatitis (“non-A, non-B, non-C hepatitis”)
   • Accounts for 40% of patients in the U.K presenting with severe acute hepatitis leading to acute liver failure (Ichai 2008, Bernal 2010)

Histological Findings
• Viral hepatitis (A-E), drugs and AIH have overlapping histological features
  ➢ Viral serology, drug history, auto-antibody serology required to identify the cause
• Other viruses rare, but have distinctive features
Acute Liver Failure due to Fulminant HSV Hepatitis

Female, age 38.

- Liver transplant for acute liver failure. Presumed accidental paracetamol overdose
- Severe IBD, treated with steroids & azathioprine. Taking paracetamol for abdominal pain

Apparently zonal necrosis and haemorrhage
  Resembles paracetamol toxicity

Coagulative necrosis (non-zonal)
Acute Liver Failure due to Fulminant HSV Hepatitis

Female, age 38.
• Liver transplant for acute liver failure. Presumed accidental paracetamol overdose
• Severe IBD, treated with steroids & azathioprine. Taking paracetamol for abdominal pain

Nuclear Inclusions
(mainly in viable hepatocytes at periphery of necrotic areas)

HSV Immunohistochemistry
Autoimmune Hepatitis - Acute Presentation

Incidence and Diagnostic Criteria

- 30-40% of cases present as acute hepatitis/acute liver failure (Czaja & Freese 2002, Lohse 2011, Gleeson 2012)
- Autoantibodies and hypergammaglobulinaemia may not be present at the time of presentation with acute AIH (Lohse 2011)

Histological Features

- Up to one third of cases have features of underlying chronic liver disease
- Remaining cases frequently have classical features of acute lobular hepatitis
- Features favouring a diagnosis of AIH (Stravitz 2011, Yeoman 2014)
  - Portal inflammation/interface hepatitis (resembling chronic AIH)
  - Plasma-cell rich inflammatory infiltrate
  - Lymphoid follicles
  - Centrilobular necrosis/central perivenulitis
Liver biopsy rarely identifies a previously unsuspected aetiology

- Biopsies mostly obtained from people in whom main recognised causes have been excluded (“seronegative hepatitis”)
- Biopsy sometimes provides aetiological pointers, including cases presenting with acute liver injury not due to acute hepatitis
  - Decompensated chronic liver disease (e.g. Wilson’s disease)
  - Another cause of acute liver damage (e.g. ischaemic necrosis, severe alcoholic hepatitis, paracetamol toxicity)
  - Hepatic infiltration (usually lymphoma, rarely carcinoma)
- Liver usually enlarged
The End