Drug-induced Acute Liver Failure

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Disclosures

I have nothing to disclose.

Acute liver failure (Fulminant hepatitis)

• Definition - onset of hepatic encephalopathy within 8 weeks of onset of symptoms

• Often accompanied by massive/submassive necrosis

Evaluating a liver biopsy for drug etiology

• Drug-induced liver injury can mimic any pattern of liver disease

• In most cases, unequivocal histological diagnosis is not possible

• Incomplete drug history and multi-drug use complicate interpretation
Drug-induced acute liver failure has 3 patterns

- Extensive microvesicular steatosis (rare)
- Necrosis with little or no inflammation
- Necrosis with marked inflammation (most common)

Pattern 1

- Extensive microvesicular steatosis (rare)
  - Ex: Tetracycline, zidovudine (nucleoside analogs), valproate, L-asparaginase, amineptine

*Diagnostic pitfall – identifying macrovesicular (large and small droplet) and microvesicular steatosis

Large and small droplet fat

True microvesicular steatosis
27-year-old man on entecavir (Baraclude)

Extensive microvesicular steatosis

- Mechanism – mitochondrial injury, may be accompanied by lactic acidosis
- Morphology – little inflammation, variable cholestasis and necrosis
- DDx – alcoholic foamy degeneration, Reye syndrome, acute fatty liver of pregnancy, Jamaican vomiting sickness (ackee fruit), urea cycle enzymatic deficiencies

Patterns 2 and 3

- Necrosis with little or no inflammation
- Necrosis with marked inflammation (most common)

Intrinsic vs. idiosyncratic hepatotoxicity

- Intrinsic toxins (relatively few drugs)
  - Necrosis with little or no inflammation
  - Damage in a predictable, dose-dependent manner by drug or its metabolite
- Idiosyncratic hepatotoxins (most drugs)
  - Necrosis with marked inflammation
  - Metabolic (predisposed individuals)
  - Immunological (hypersensitivity)
Pattern 2

- Necrosis with little or no inflammation
  - Ex: Acetaminophen, cocaine, MDMA (Ecstasy), CCl₄, mushroom alkaloids

Acute acetaminophen toxicity

- Acute coagulative, perivenular (zone 3) to panacinar necrosis
- Minimal to no inflammation; no fibrosis

Pattern 3

- Necrosis with marked inflammation (most common)
  - Ex: Antimicrobials, MAO inhibitors, anticonvulsants, herbal and supplemental agents, potentially any drug that causes acute hepatitis

Acute hepatitis

- The most common drug-related injury pattern seen on biopsy
  Rest of differential
  - Acute viral hepatitis
  - Initial presentation of autoimmune hepatitis
  - Wilson disease
  - Up to 15% of cases progressing to fulminant hepatic failure are of unknown etiology
Ketoconazole toxicity

Submassive to massive necrosis

- Early stage — necrosis
- Subacute to late stage — regeneration with nodule formation

*Diagnostic pitfall: distinguishing necrosis from fibrosis in persistent drug injury

Severe active (subacute) hepatitis with diffuse small nodules mimicking cirrhosis

Distinguishing fibrosis from necrosis

Trichrome stain
- Established fibrosis is uniformly dark blue
- Elastic fiber bundles appear pale

- Necrosis shows two-toned staining
  - Dense, darker, and thicker bundles of scar
  - Light, loose, and thinner bundles of residual framework and debris
Trichrome, Cirrhosis

Severe acute hepatitis, trichrome: subacute stage
Fibrosis vs Necrosis

Reticulin stain
- Highlights cell plate framework
  - Regenerative plates
  - Collapsing plates
  - No distinct staining pattern for established scar
Fibrosis vs Necrosis

Elastic stains – Orcein

• Highlights elastic fibers in later stages of fibrosis, as well as smaller elastic fibers in early stages of fibrosis
Orcein in cirrhosis with elastic bundles

Subacute hepatitis with prominent ductular reaction

Orcein, Subacute Hepatitis

The only elastic fibers present are in residual portal zones or central veins

Histochemical stains

<table>
<thead>
<tr>
<th></th>
<th>Necrosis</th>
<th>Fibrosis</th>
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<tbody>
<tr>
<td>H&amp;E</td>
<td>Dropout</td>
<td>-</td>
</tr>
<tr>
<td>Trichrome</td>
<td>Two-tone blue Thin fibers</td>
<td>All dark blue Thicker bundles</td>
</tr>
<tr>
<td>Reticulin</td>
<td>Dropout/Collapse</td>
<td>-</td>
</tr>
<tr>
<td>Orcein (elastic fibers)</td>
<td>Negative</td>
<td>Positive</td>
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Phenytoin-induced hepatitis

Lamotrigine-induced hepatitis

Isoniazid-induced hepatitis

Drugs that can mimic autoimmune hepatitis

- Methyldopa  ANA (16%), ASMA (35%)
- Minocycline  ANA, anti-DNA
- Nitrofurantoin  ANA (80%), ASMA (72%)
- Oxyphenisatin  ANA (67%), ASMA (67%)
- Statins  ANA (80-90%) ASMA (25%)
Methyldopa hepatitis

Possible drug injury – herbals

Herbals & supplements

- An often overlooked source of liver injury
- Not regulated by the FDA
- >20,000 products marketed as powders, essential oils, teas
- $5 billion spent annually purchasing herbals
- Nearly 20% of Americans have used herbals
- Herbal supplements may be contaminated by heavy metals (arsenic, lead, mercury, cadmium)
Drug injury can mimic any pattern of primary liver disease
- Careful clinical history is essential (including herbals)
- Literature search can be useful

Acute liver failure (morphologic correlate of fulminant hepatitis) has 3 patterns:
- Extensive microvesicular steatosis
- Necrosis with little inflammation
- Or necrosis with marked inflammation