Acute Hepatitis / Acute Liver Failure

Liver and Gastrointestinal Pathology Update
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Major causes of acute hepatitis and acute liver failure

- Viral hepatitis
- Drugs, herbals and toxins
- Autoimmune hepatitis
- Metabolic disease
- Vascular disease

Clinical manifestations of acute hepatitis

- Elevated aminotransferases
  - AST and ALT
- Relatively mild elevation in alkaline phosphatase
- Jaundice
- Viral hepatitis prodrome
  - nausea, vomiting, anorexia, myalgia, malaise

Clinical manifestations of acute liver failure

- Markedly elevated AST and ALT
- Relatively mild elevation in alkaline phosphatase
- Jaundice
- Coagulopathy – INR greater than 1.5
- Ammonia
- Ascites
- Encephalopathy
- Renal failure
Acute liver failure
• Definition
  • Coagulopathy and encephalopathy developing in 6 months or less

Fulminant hepatic failure
• Definition
  • Liver dysfunction, progressing from initial symptoms to hepatic encephalopathy in 2 - 3 weeks
  • Most cases are caused by massive hepatic necrosis

Subfulminant hepatic failure
• Definition
  • Liver dysfunction, progressing from initial symptoms to hepatic encephalopathy in approximately 3 months
  • Most cases are caused by submassive hepatic necrosis

Non-necrotic acute liver failure
• There are a handful of conditions which result in acute liver failure but have little or no hepatocellular necrosis
  • Microvesicular steatosis syndromes
Viral Hepatitis

- Systemic viruses, which in most cases do not involve the liver, can occasionally be associated with clinically evident hepatitis
  - EBV
  - CMV
  - Herpes simplex
  - Adenovirus

EBV mononucleosis

- Biopsy is only performed when EBV has not been recognized or when there are confounding clinical findings
  - Portal and sinusoidal lymphocytes
  - Sinusoidal infiltrate may be striking
  - Can suggest lymphoma or leukemia
    - particularly if the lymphocytes are atypical

EBV vs Usual Viral Hepatitis

- Hepatocellular injury is usually mild, inconspicuous and focal
- Cholestasis - mild or absent
- The extensive sinusoidal infiltrate in conjunction with mild hepatocellular injury allows distinction from most cases of usual acute viral hepatitis
  - IHC for LMP
  - in situ hybridization for EBER RNA

Case History

- 4 year old with history of ALL
- Remission for 1 year
- Presents with hepatosplenomegaly, fever and elevated transaminases
CMV hepatitis

- Biopsy is only performed when CMV has not been recognized or when there are confounding clinical findings
- Hepatitis is accompanied by a generalized viral illness
  - Lobular lymphocytic infiltrate similar to EBV but should be less striking
  - No viral inclusions
  - IHC negative
- Viral inclusions are seen only in immune compromised patients

Herpes simplex

- Generally considered an opportunistic infection
- Rare cases of severe liver disease in immune competent patients
- The histologic diagnosis is generally straightforward
  - Focal or massive necrosis
  - Not zonal
  - Neutrophilic infiltrate
  - Viral inclusions are usually but not always evident
  - IHC is confirmatory

Clinical history

- 16 year old, collapsed playing football, parents consented to donation of organs
- Surgeon - “liver looks funny”
- Donor liver frozen section (middle of the night)
- Dx: focal necrosis, no steatosis
Clinical history

- 16-year-old female in fulminant liver failure
- Please evaluate for toxic, autoimmune, infection or metabolic etiology
Subsequent case history

- 2 days of fever, edema involving the face and the extremities, dyspnea and chest pain
- Presumed diagnosis of angioedema
  - Treated with high dose solumedrol for 7 days for
- Developed lethargy, progressed to fulminant hepatic failure in 24 hours
Clinical history

- Autopsy demonstrated herpetic lesions on gingival and on labial mucosa
- Acute Herpes simplex infection treated with high dose steroids

Adenovirus

- Common pathogen
  - respiratory tract, GI tract
- HIV and bone marrow transplantation
  - Fulminant hepatic failure
    - Children and adults
- Liver transplant
  - Rare cause of hepatitis in children
    - Very rare in adults

Adenovirus - histology

- Variable findings
- Generally smudgy inclusions
  - Less discrete than CMV, but occasionally well formed
- Focal coagulative necrosis with variable inflammation
Bone marrow transplant patient with fulminant hepatic failure

Acute viral hepatitis

A B C D E

- Biopsies are rarely performed
- If the diagnosis has not been established by viral serology
- When there is conflicting or confusing clinical information
- In order to determine whether there is chronic disease
Acute hepatitis

- Most patients who do undergo liver biopsy for acute liver dysfunction have a process other than acute viral hepatitis
  - autoimmune hepatitis
  - drug/herbal hepatitis

Incidence of acute hep A and B is declining in U.S.

- Incidence of acute hepatitis A has declined 92%
  - 1995 - 12.0 per 100,000
  - 2007 - 1.0 case per 100,000
  - successful vaccination programs
- Incidence of acute hepatitis B has declined 82%
  - 1990 - 8.5 cases per 100,000
  - 2007 - 1.5 cases per 100,000
  - successful vaccination programs
  - successful blood product screening

Incidence of acute hepatitis C is declining in U.S.

- New hepatitis C infections in late 1980’s
  - approximately 230,000/yr
- New hepatitis C infections in 2004
  - approximately 26,000/yr
- Successful blood product screening
- Currently there is no vaccination

Acute Hepatitis D

- Requires Hepatitis B for replication
- Can cause acute hepatitis
  - coinfection with hepatitis B
  - superinfection of a patient with chronic hepatitis B
- Serology and immunohistochemistry are available

Fulminant hepatic failure from viral hepatitis

- Hepatitis B - most common viral cause of fulminant hepatic failure in the U.S.
  - acute infection
  - reactivation of chronic hepatitis
    - immunosuppression
    - chemotherapy for lymphoma/leukemia
    - gleevac
  - development of core mutant
- Hepatitis A and B cause approximately 12% of the fulminant hepatic failure in the U.S.

Acute Hepatitis C

- Acute Hepatitis C
  - most infections are subclinical
  - Symptomatic in 15%
    - rarely if ever causes fulminant hepatic failure in U.S.
  - One third of symptomatic patients have undetectable antibody at start of symptoms
    - PCR for HCV RNA will be positive

Acute Hepatitis E

- Rarely causes clinical disease in U.S.
  - waterborne acute hepatitis in developing countries
  - most severe in third trimester of pregnancy
- Seroprevalence in U.S. - 21.0% from 1988 through 1994
  - different genotype than in developing countries

Acute viral hepatitis

- The histologic features are similar with a few unreliable exceptions
- Distinction is based on serologic studies
- Similar findings in many cases of drug induced hepatitis
Histology of acute viral hepatitis

• Active hepatocellular injury and necrosis
  • Ballooning degeneration
  • Apoptosis
  • Lobular disarray – the normal plate architecture is obscured by…
    • Hepatocellular swelling
    • Small foci of stromal collapse
    • Regenerative widening of plates
    • Cholestatic rosettes
Severe acute hepatitis

- Confluent necrosis
  - clusters of necrotic hepatocytes
  - random
  - zone 3 or zone 1
- Bridging necrosis
  - central to portal - severe zone 3 necrosis
  - portal to portal - severe zone 1 necrosis
  - generally does not involve all lobules equally
- Panlobular/acinar necrosis – bridging necrosis that involves the entire lobule

Histology of Acute Viral Hepatitis - Inflammation

- Lymphocytic
  - fewer neutrophils, eosinophils, plasma cells
- Predominantly lobular
- Portal inflammation is often sparse
- Prominent perivenular inflammation in many cases
  - central vein “phlebitis”
- Kupffer cell hypertrophy
Acute hepatitis - histology con’t

- Hepatocellular regeneration
- Mitosis, binucleate cells, and focally thickened hepatocellular plates
- Bile
  - When extensive may be accompanied by a ductal reaction/proliferation
- Fatty change +/-

Resolution of acute hepatitis

- Lobular Inflammation recedes
  - portal inflammation may remain longer (r/o chronic)
- Swollen and necrotic hepatocytes recede
- Regenerative activity increases
- Clusters of enlarged Kupffer cells remain
Resolution of acute hepatitis

- Resolving acute hepatitis may resemble chronic hepatitis
- 6 month rule
  - the definition of chronic viral hepatitis requires elevation of AST/ALT or positive viral markers for more than 6 months
  - most cases of acute viral hepatitis have resolved by 6 months

Acute viral hepatitis
A vs. B vs. C

- **Hepatitis A**
  - may have prominent portal infiltrates with numerous aggregates of plasma cells
  - extensive zone 1 necrosis
Acute viral hepatitis  
A vs. B vs. C  

- **Hepatitis B**  
  - IHC for HB surface Ag and core Ag is frequently negative in acute hepatitis B  
  - ground glass hepatocytes are not generally seen  
    - more common in chronic hepatitis  
  - Consider hepatitis D if the appearance is of acute hepatitis in a patient with a history of chronic HBV  
    - IHC for delta agent may be positive  

- **Hepatitis C**  
  - May have prominent sinusoidal infiltrates without extensive hepatocellular injury  
  - Prominent Kupffer cell aggregates  
  - Duct infiltration and injury
Differential diagnosis

**Acute hepatitis**
- Marked elevation AST/ALT with mild elevation of alkaline phosphatase
- Lobular disarray
- Foci of stromal collapse and regeneration
- Perivenular inflammation, zone 3 necrosis

**Bile duct obstruction**
- Marked elevation of alkaline phosphatase with mild elevation of AST/ALT
- Periductal edema/fibrosis
- Maintained plate architecture
- Copper or Copper binding

16 y.o. with acute jaundice 6 weeks after trip to china
**Differential diagnosis**

**Autoimmune hepatitis**
- Serology
- Prominent portal infiltrates
- Prominent plasma cell component
- Interface activity
- Bile duct infiltration/injury

**Drug induced hepatitis**
- Serology/History
- Granulomas
- Eosinophils
- Duct injury
- Severe cholestasis/canalicular cholestasis
- Syncitial hepatocytes
- Marked steatosis

**Acute hepatitis**
- Lobular disarray
- Perivenular inflammation or phlebitis
- Zone 3 necrosis
- Stromal collapse
- Liver failure in a noncirrhotic

**Chronic viral hepatitis**
- 6 month rule
- Dense portal aggregates
- Prominent interface activity
- Fibrosis
Syncitial giant cells in presumed herbal vitamin induced hepatitis

Differential diagnosis

Steatohepatitis
- Steatosis – zone 3
- Mallory bodies – zone 3
- Fibrosis - zone 3
- Neutrophils

Clinical history

- 25 year old male
- Elevated LFT's
- Rule out autoimmune hepatitis
Clinical history

- Dx – Hepatitis with moderate activity (grade 3 of 4)
- No fibrosis
- Comment: serologic studies are required…….

Subsequent history

- Hepatitis A IgM +
Clinical history

- 35 year old woman, 4 months post partum
- Elevated AST, ALT
- HCV, HBV serologies negative
- ANA 1:80; SMA negative
- Minimally elevated globulins
- Clinical dx – rule out AIH

Diagnosis

- Hepatitis with moderate lobular activity (grade 3 of 4)
- No fibrosis (0/4)
- Comment: Findings are compatible with but not typical of AIH. Complete serologic workup and clinical history to rule out drug/herbal hepatitis recommended
Subsequent history

- PCR for HCV RNA positive

Collapse vs. fibrosis

- Extensive loss of hepatocytes results in collapse of parenchyma and reticulin network
- May be difficult to distinguish from fibrosis
- Radiologic studies may incorrectly indicate cirrhosis due to the effect of regenerative parenchyma alternating with areas of collapse

Collapse vs fibrosis

- Trichrome and reticulin stains can be challenging
- Comparison of mature collagen in portal areas and around veins with the areas of collapse within the lobules
- Other stains which may be helpful but are not routinely performed in most laboratories
  - orcein, victoria blue and Sirius red.
trichrome in subfulminant

Victoria blue in subfulminant
Patterns of drug induced liver injury

- Acute hepatitis
- Chronic hepatitis
- Zonal necrosis
- Bland cholestasis
- Idiosyncratic drug induced cholestasis
- Bile duct obstruction
- Steatohepatitis
- Vascular disease

Drug induced hepatitis

- Acute hepatitis may be similar in appearance to acute viral hepatitis
  - Serologic studies to rule out viral hepatitis must be performed
- Eosinophils, granulomas
- Duct injury
- Syncitial hepatocytes
- Marked steatosis

Idiosyncratic Drug Induced Hepatitis

- Some of the more common causes
  - Halothane
  - Isoniazid
  - Chlorpromazine
  - Nitrofurantoin
  - Augmentin
  - Troglitazone (Rezulin)
    - oral hypoglycemic pulled from the market due to severe hepatitis
Drug induced hepatitis and autoantibodies

- Rarely associated with autoantibodies
  - may initiate an autoimmune hepatitis
- Best known example
  - minocycline - tetracycline derivative used to treat acne
Herbals

- same mechanisms as “traditional” drugs
- unregulated manufacture and sale
  - no controlled trials
  - purity and concentration are variable
  - difficult to predict which substances are associated with liver injury and what dosage is toxic

Zonal necrosis

- Acetaminophen toxicity
- The most common cause of fulminant hepatic failure in the U.S.

Acetaminophen toxicity

- Zone 3 coagulative necrosis
  - Zones 1 and 2 in more severe cases
- Mild predominantly neutrophilic inflammation
- Zone 3 steatosis may indicate underlying fatty fatty liver disease
- With time, disappearance of necrotic hepatocytes, Kupffer cell hypertrophy
- Ductal at interface between viable and necrotic parenchyma
Zone 3 necrosis differential diagnosis

- Acetaminophen toxicity
- Amanita phalloides (mushroom)
- Carbon tetrachloride
- Severe ischemic injury (shock liver)

Acute failure without extensive hepatic necrosis

- Microvesicular steatosis syndromes
  - Reye syndrome
  - Valproic acid toxicity
  - Intravenous tetracycline toxicity
  - Acute fatty liver of pregnancy (AFLP)
  - Congenital mitochondrial disorders
Reye’s syndrome

Acute fatty liver of pregnancy

Reye’s syndrome
Oil red O

Acute fatty liver of pregnancy