I HAVE NOTHING TO DISCLOSE

Linda Ferrell

CURRENT ISSUES IN ANATOMIC PATHOLOGY 2017

PITFALLS IN THE DIAGNOSIS OF MEDICAL LIVER DISEASE WITH TWO CONCURRENT ETIOLOGIES

Linda Ferrell, MD, UCSF

THE PROBLEM for liver pathology in 2017

IDEAL versus REAL

IDEAL = one disease only to consider
REAL = more than one entity is increasingly of concern

The Problem: Ideal vs. REAL

- Entities such as non-alcoholic steatohepatitis and HCV are relatively common
- Many patients with chronic liver disease history are living longer due to more advanced therapies (HCV, HBV, PBC)
- Risk of acquiring a 2nd etiology is likely increased over time
- Separation of entities enables better treatment with etiology-specific therapies
Where to Begin?

Recognize Major Patterns of Disease

Portal-Based or Central-Based

Acute versus Chronic Injury

Major Patterns of Disease: Portal-based

Injury typically in portal/periportal areas

- Chronic viral hepatitis, other chronic hepatitides
  - HBV, HCV, alpha-1-antitrypsin, Wilson’s, AIH
- Biliary tract obstructive disease:
  - Obstruction, primary biliary cholangitis, primary sclerosing cholangitis
- Hemochromatosis

Portal-Based: Chronic Hepatitis

Portal-Based: Chronic biliary disease (PBC) with ductular reaction in portal zones
**Portal-based: Hemochromatosis**

Iron overload begins in periportal zone. Results in periportal fibrosis due to FE toxicity.

---

**Major Patterns of Disease: Central-based**

*Injury typically in centrizonal areas*

- **Steatohepatitis**
  - Nonalcoholic (NASH), Alcoholic
- **Chronic ischemic injury and/or chronic vascular outflow obstruction**
  - Budd-Chiari syndrome, congestive heart failure
- **Some mild to moderate acute drug/toxic injuries**
  - Acetaminophen, mushroom toxicity

---

**NASH, Trichrome: Centrizonal pericellular and sinusoidal fibrosis**

---

**Central-based: Chronic Venous Outflow Obstruction**

- Chronic Heart Failure
- Chronic Budd Chiari Syndrome
Central based: Toxic (one-hit) event
Example: Acetaminophen

Central-Based Pattern: Pitfalls

*Chronic* changes of centrizonal region that can mimic portal tracts, so called “portalization of central zones”

- **Arterialization** within centrizonal scar
- **Ductular reaction/metaplasia** of injured hepatocytes and/or progenitor cells

*NASH, Trichrome: Centrizonal Fibrosis (1b)*

Arrows highlight centrizonal arteries

*DON’T CONFUSE WITH PORTAL ZONE*
Budd-Chiari Syndrome: Centrizonal Fibrosis and Ductular Metaplasia

Don't confuse with portal zone

Where to Begin?
Recognize major patterns of disease
1. Portal-based versus central-based
2. Acute versus chronic injury

Acute or chronic injury

Major patterns:
- Hepatocyte panlobular injury
  - Inflammatory (hepatitic) panlobular
  - Necrotic panlobular
- Fatty change
  - Alcohol, Non-alcoholic steatohepatitis, other causes
- Fibrosis versus necrosis
  - Biggest issue is cirrhosis versus severe active hepatitis with regenerative nodules and intervening necrosis

Hepatocytic panlobular injury

- Inflammatory (hepatitic) panlobular
  - Acute hepatitis (notable examples: HAV, HEV, AIH, idiosyncratic drug or “herbal” reactions)
  - Ongoing/active chronic hepatitis (examples: AIH, HBV, HCV)
- Necrotic panlobular: acute injury with minimal inflammation
  - Toxic (one-hit, as with acetaminophen)
  - Ischemic (example: shock)
- Combination of inflammatory and necrotic
  - Severe acute to subacute hepatitis (more variable stages of necrosis + inflammatory changes usually with ductular reaction)
Fibrosis versus Necrosis

Routine histochemical stains can be helpful
- Trichrome: Two-toned color and two textures
  - Scar: darker blue color and dense fibers
  - Necrosis: Lighter blue color and more delicate fibers
- Reticulin: collapsed or not
- Orcein/EVG: Used for elastic fibers; formation starts about 12 weeks after injury


Severe Acute Hepatitis, Inflammatory Pattern

Generally presents as fulminant liver failure
Typically correlates with submassive to massive necrosis of the liver
- Early stage — necrosis, Kupffer cell reaction
- Subacute stage — hepatocyte regeneration, early collapse of reticulin framework
- Late stage — nodule formation; fibrosis and/or cirrhosis

EARLY Severe Acute Hepatitis:
Necrosis and Kupffer Cell Reaction

Panlobular necrosis and congestion
Immunostain for CD68 to confirm as Kupffer cells

EARLY Severe Acute Hepatitis:
Necrosis and Kupffer Cell Reaction

Trichrome: No hepatocytes; Centrilobular zone, two colors and textures
Light and delicate = necrosis
Dark and Dense = Normal structures or scar

Reticulin stain: Centrilobular zone, framework still intact
Intact plates, No necrosis
Intact plates: Necrosis
Subacute Severe Hepatitis: Regeneration and collapse

- Nodular regeneration, congestion of necrotic centrilobular zones
- Reticulin stain: Collapse of framework between regenerative nodules
- Regenerative nodule
- Congested central zone
- Collapse: Thinner plates, wavy fibers

Subacute Severe Hepatitis

- Trichrome stain: Lighter blue with congestion, ductular reaction = zones of recent necrosis
- NODULAR regeneration and DUCTULAR REACTION indicates subacute process

Late Stage: Established Cirrhosis

- Trichrome: Dark, dense blue scar
- Orcein: Elastic (black) fibers as sign of chronicity

Late Stage: Established Cirrhosis

- Orcein: Elastic fibers in Cirrhosis
In contrast: Acute Necrosis, <12 weeks in duration

Orcein: Elastic (black) fibers present in residual portal tracts and central veins; ductular reaction present

In contrast: Subacute injury approaching 12 weeks

Orcein: Elastic (black) fibers limited to portal zones, central veins; rare small fibers in early scar

Regenerative nodule

Late Stage: Established Cirrhosis

Trichrome: Dark, dense blue scar and pale grey zones (Elastic fibers)

Elastic (EVG) stain: Black elastic fibers

Late Stage: Established Cirrhosis

Trichrome: Dark, dense blue scar and pale grey zones (Elastic fibers)

Orcein stain: Black elastic fibers
**Question: Fibrosis or Necrosis**

Is this centrilobular fibrosis or necrosis on trichrome stain?

- A. Fibrosis
- B. Necrosis

**Mixed etiology: Acute on Chronic**

**CASE 1**
- 31 year old man, history of ulcerative colitis
- Clinical diagnosis of primary sclerosing cholangitis in 2001, no liver biopsy
- No signs of cirrhosis 3 months prior to his presentation of subacute liver failure with high levels AST, ALT
- Transplanted at UCSF
- Clinical diagnosis: Possibly end-stage PSC, but an unusual rapid hepatitic pattern of progression over 3 months

**Acute on Chronic**

Large zones of panacinar necrosis, with ductular reaction and inflammatory infiltrates

**Acute on Chronic**

Trichome: zones of collapse, but no dark bands of fibrosis

Trichrome stain: Two toned, light and dark
**Acute on Chronic**

- Focal regenerative nodules
- Trichrome: No fibrosis

**Question: What is your best diagnosis?**

A. Cirrhosis due to HCV and primary sclerosing cholangitis (PSC)
B. Acute hepatitis and PSC
C. Chronic hepatitis C and PSC
D. Fatty liver disease (NASH) and PSC
**Mixed Etiology: Acute on Chronic**

**DIAGNOSES**
- Chronic changes of early stage PSC
  - Periduct fibrosis and hilar duct sclerosis
- Superimposed acute hepatitis of unknown etiology
  - Zones of panacinar necrosis, without fibrosis

---

**Case 2**
- 50 year old obese man, diabetic and heavy drinker
- No previous liver biopsy
- Presented in liver failure and ascites for liver transplantation
- *Clinical diagnosis:* End-stage liver disease, possibly due to severe steatohepatitis

Case courtesy of Dr A Paul Dhillon, Royal Free Hospital, London

---

**Acute on Chronic**

- **Trichrome:** nodular, with necrosis, two toned
- Focal bridging fibrosis involving centrizonal areas, mild fatty change

---

**Acute on Chronic**

- Two toned; and swollen, ballooned hepatocytes
- Two toned; with ductular reaction, focal fat, ballooned hepatocytes
Question: What is your best diagnosis?

A. End-stage cirrhosis due to steatohepatitis
B. Steatohepatitis with fibrosis, with overlying acute injury

Mixed etiology: Acute on Chronic

- Chronic steatohepatitis with bridging fibrosis, indistinguishable for NASH or ASH
- Overlying acute hepatitis, not specific for etiology, plasma cells seen

Differential diagnosis: AIH, Drug, HAV, HEV

Workup: negative for autoimmune markers, HAV, and drug/herbal/other nutritional agents

Final Diagnosis: Hepatitis E (HEV) and chronic steatohepatitis
Acute on Chronic: *Same Disease*

**Usual suspects**
- AIH, more common in women
- Exacerbation of HBV
- Wilsons disease in younger patients

*Example: Wilsons Disease*

Mixed Etiology: Chronic on Chronic

**Most commonly: NASH + HCV or HBV**
- Prominent chronic inflammation in NASH may suggest superimposed viral or other hepatitis/inflammatory process, but scattered plasma cells normal in NASH
- CAVEAT: Chronic inflammation can be increased and fat may be decreased in Stage 3-4 NASH

NASH + HCV or HBV

**NOTE pattern of disease locations**
**PORTAL:** favors chronic hepatitis
- Portal-based chronic inflammation, fibrosis, and interface hepatitis
- HBV or HCV markers
**CENTRAL:** favors steatohepatitis
- Centrizonal fat, fibrosis, ballooned cells, inflammation associated with fat
- Risk factors for NASH/ASH

NASH and HCV

Cirrhotic and periportal fibrosis
**NASH and HCV**

**Centrizonal and Periportal fibrosis**

**How to stage?**

**NASH + HCV or HBV STAGING**

For earlier stages, stage separately, if possible
- NASH: Brunt or Kleiner stage
  - Case example
    - if all fibrosis due to NASH, Stage 2 NASH
    - If periportal likely due to HCV, then Stage 1 NASH
- Viral hepatitis: Do not include central fibrosis
- Note prominent pattern or combination of patterns as centrizonal or portal if possible

**NASH and HCV, stage 4**

**NASH and HCV**

- Ballooned Hepatocytes, mild fat
- Lymphocytic infiltrate could be HCV
NASH and HCV, cirrhosis

How to stage for late stages?

NASH + HCV or HBV STAGING

- Later stages: 
  - Stage combined etiologic patterns as bridging fibrosis or cirrhosis
  - Stage 3 or 4
  - Note if both centrizonal, portal patterns are present, and if possible, most prominent pattern
  - Note any difficulties of determining etiologic cause of all fibrosis to communicate the message that both entities could have contributed to stage

Mixed Etiology: Chronic on Chronic

Case 3
- 58 year old obese woman with diabetes
- Followed for NASH for 5 years
- Presents now with elevated alkaline phosphatase and itching
- Liver biopsy performed at UCSF

Chronic on Chronic

Classic centrizonal NASH changes: Fat, Ballooned hepatocytes
Trichrome stain: Centrizonal, pericellular fibrosis
Chronic on Chronic

Trichrome:
Central to central bridging fibrosis typical of stage 3 NASH

PORTAL:
Lymphoid aggregate and granulomatous infiltrate, plus damaged dilated duct

Chronic on Chronic

Trichrome:
Left: Central fibrosis
Right: periportal fibrosis with prominent inflammatory nodule

PORTAL:
Granulomatous infiltrate extending into lobule, plus duct loss
Question: What is your best Diagnosis?

A. NASH and HCV  
B. NASH and primary sclerosing cholangitis  
C. Fatty liver without NASH, and sarcoidosis  
D. NASH and primary biliary cholangitis

Mixed etiology: Chronic on Chronic

- Granulomatous infiltrates and duct injury/loss not typical of NASH, suggesting primary biliary cholangitis
- Patient found to have high titers AMA

Final Diagnoses:
- Chronic steatohepatitis with bridging fibrosis  
- Overlying primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, early stage

Take home messages

- Recognize Major Patterns of Disease  
  - Portal-based, Central-based, Acute vs Chronic  
- Use special stains to recognize Acute versus Chronic  
  - Trichrome, Reticulin, Elastic stain  
- Importance of clinical correlation  
  - Includes history of duration of illness, therapies/drug exposures, risk factors for common liver diseases, and laboratory workup