Nonalcoholic Fatty Liver Disease
Update in Pathology
September 3, 2009
Elizabeth M. Brunt, MD
Department of Pathology
and Immunology

"The Fat Lady"...

Challenges/Opportunities in NAFLD 2009

Human appetite is elastic: give us more and we'll eat more.

THE NEW YORKER, JULY 30, 2009
Challenges in NAFLD

- The Clinicians
- The Pathologists
- The Liver
- The Disease Itself

Value of Liver Biopsy in NAFLD: “Contentious and Controversial”

- Pro’s
  - Confirm diagnosis
  - ...exclude other causes of liver dysfunction

- 354 pts with unexplained liver test abnormalities
  - Fatty liver: 66% (SH with fibrosis, 32%)
  - PBC, PSC, sarcoid, AIH, HH: 5.1%
  - Drug-related: 7.6%
  - Cryptogenic: 9%

Skelly MM. J Hepatol 2001;35:195-199
Bianchi L. J Hepatol 2001;35:290 (Editorial)
• 354 pts with unexplained liver test abnormalities
  – Fatty liver: 66% (SH with fibrosis, 32%)
  – PBC, PSC, sarcoid, AIH, HH: 5.1%
  – Drug-related: 7.6%
  – Cryptogenic: 9%

  – Normal liver: 5.9%


Value of Liver Biopsy in NAFLD

• 52 y/o overweight man
  • ALT 77 IU/L (4xULN)
  • negative serologies, no medications
  • negative alcohol hx
  • US: “fatty liver”

Clinical, histologic features in “atypical” settings

• Concurrent with other forms of liver disease
  – Hepatitis C (5-10%)
    Ong, Liver 2001; Brunt, Mod Pathol 2003; Sanyal, Am J Gastroenterol 2003
  – Primary Biliary Cirrhosis, AIC, HBV, AIH, α1AT (~5%)
    Brunt, Mod Pathol 2003; Sanyal, Am J Gastroenterol 2003; Sanchez-Munoz, Dig Dis Sci 2004

• Some drugs, occupational toxins/exposures
  Farrell, Semin Liv Dis 2002; Catriona, Liver 1999; JAMA 2005
Value of Liver Biopsy in NAFLD: “Contentious and Controversial”

- **Pro’s**
  - Confirm diagnosis
  - Intra-op visuals do not correlate with disease severity
  - ALT in not reliably elevated

Normal ALT

- **Entire histologic spectrum: steatosis to “silent” cirrhosis**
  - 12% cirrhosis
    - Mofrad, Hepatology 2003
  - 10% cirrhosis
    - Sorrentino, J Hepatol 2004
  - 8% cirrhosis
    - Fracanzani, Hepatology 2008
  - 40% Stages 1-3 fibrosis (peds):

Normal ALT

- **Steatosis grade**
  - elevated ALT (p=0.0001)
- **Necroinflammation grade**
  - elevated ALT (p=0.0002)

- **Fibrosis scores**: no signif difference b/w groups

Value of Liver Biopsy in NAFLD: “Contentious and Controversial”

- **Pro’s**
  - Confirm diagnosis
  - Intra-op visuals do not correlate with disease severity
  - ALT in not reliably elevated
  - Evaluation:
    - Severity of injury
    - Fibrosis/Architecture
Value of Liver Biopsy in NAFLD: “Contentious and Controversial”

- **Pro’s**
  - Confirm diagnosis
  - Intra-op visual deemed correlate with disease severity
  - ALT is not reliably elevated
  - Biopsy evaluating:
    - Severity of injury
    - Fibrosis/Architecture

- **Con’s**
  - Invasive, potentially harmful
  - There is no treatment to offer
  - Most "suspected" patients "only" have NAFLD
  - Imaging and noninvasive markers are improving

“Problems” with Liver Biopsy

- 10-30 mm length x 1.2mm diameter
- ~10 portal tracts
- ~1/50,000 – 1/63,000 of liver parenchyma

Chronic Hepatitis:
- Sample size is important in grading, staging
  - Redosta, Hepatology 2003;38:1449
  - Colloredo, J Hepatol 2003;39:239
  - Guido, Semin Liv Pathol 2004;24:89

Fatty Liver Disease:
- Variability of lesions within the liver alters grade and stage;
  - size (length and width) matters
  - Dixen, Gastroenterol 2001;121:91
  - Ratziu, Gastroenterol 2005;128:1898
  - Goldstein, Anatomic Pathology 2005;123:382
  - Merriman, Hepatology 2006;44:844
  - Larson, Clin Gastro Hepatol 2007;5:1329
  - Vuppala, Clin Gastro Hepatol 2009;7:481

The Pathologists

- Specimen adequacy…sampling concerns
- How good are we?
- Understand the disease process(es), nuances in histologic diagnoses

Lee, RG (ed), *Diagnostic Liver Pathology*. St. Louis, Mosby, 1994, Ch 1.
Variability of Findings in NAFLD

Sampling “Error”

- 51 patients
- 2 simultaneous cores
- processed and interpreted separately

Ratziu et al, Gastroenterol 2005;128:1898

Hierarchy of hepatic portal tracts and bile ducts

Fibrosis Evaluation…Sampling Considerations

Intra-operative Biopsy
Bariatric Surgery

- Almost no steatosis
- Variability of Portal Tract Size

Scheuer and Lefkowitch, 6th ed, 2006  Courtesy Dr. Jay Lefkowitch

Scheuer and Lefkowitch, 6th ed, 2006
Are studies that compare percutaneous bx with operative bx comparing “Apples v Oranges”? 

**The Pathologists**

- Specimen adequacy…sampling concerns
- **How good are we?**
- Understand the disease process(es), nuances in histologic diagnoses

**Interobserver Variability Studies**

“Sections of the liver biopsy show....”
**Interobserver Variability Studies**

<table>
<thead>
<tr>
<th>Adult or Pediatric</th>
<th>n # Pathologists</th>
<th>Steatosis</th>
<th>Fibrosis</th>
<th>Ballooning</th>
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**Interobserver Variability Studies**

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**The Pathologists**

- Specimen adequacy...sampling concerns
- How good are we?
- Understand the disease process(es), nuances in histologic diagnoses
Case Review: 58 y/o man

Obese, elevated HbA1c (7.7), ALT 59 IU/L, AST 76 IU/L
“Mild” alcohol use

Dx: Steatohepatitis, history of obesity, diabetes and alcohol use
Marked activity, grade 3
Need trichrome stain for proper staging, but beyond stage 1

ALD and NAFLD
…a few facts and figures…

<table>
<thead>
<tr>
<th>ALD</th>
<th>NAFLD (in obese)</th>
</tr>
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<tbody>
<tr>
<td>Develop related liver disease</td>
<td>&lt; 15% of heavy drinkers</td>
</tr>
<tr>
<td>Genetic/familial associations for liver disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Ethnic/Social disparities</td>
<td>Religious and Cultural Stigmata</td>
</tr>
<tr>
<td>Age, Gender differences</td>
<td>Not in very young or very old; W&gt;M</td>
</tr>
<tr>
<td>Major risk factors</td>
<td>Amt in past 10-20 yrs; pattern of consumption (meals v only weekends) (types of beverages); central obesity, acetaminophen use; GENES</td>
</tr>
</tbody>
</table>

Risk of NASH: female; T2DM; environment, diet, GENES
**ALD and NAFLD**

**ALD**
- Reversibility: Difficult, unlikely
- Morbidity: Alcoholic hepatitis; complications of cirrhosis
- Affects on HCV co-infection: Increases progression of fibrosis
- Increase fibrosis in HCV: Yes
- Long-term risk of cirrhosis and complications: OLT
- Proportion of Chronic Liver Disease in US: 1-2%

**NAFLD (in obese)**
- Reversibility: Difficult, unlikely w/out bariatric surgery
- Morbidity: Many assoc diseases; CVD, sleep apnea, PCOD; Obesity-related malignancies
- Affects on HCV co-infection: Co-factor in progression
- Increase fibrosis in HCV: Yes
- Long-term risk of cirrhosis and complications: OLT
- Proportion of Chronic Liver Disease in US: 5-15%

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**AFLD**

**NAFLD**

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**Same Pattern....? Subtle Differences in Types of Collagen?**

**Steatohepatitis, Diabetes**

**Steatohepatitis, Alcohol**

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**Nakano, Hepatol Res. 2005;33:210**
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<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td>Alcoholic Foamy Degeneration</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
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<td>Burned-Out Cirrhosis</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
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**New Discussions in NAFLD Pathology**

- Steatosis is dynamic
- Acidophil bodies/apoptosis as marker
- Ballooning: can we better characterize this
- Portal inflammation: how does it relate
- Fibrosis in NAFLD: role of HPC
Hepatic Steatosis: Role of PAT

**PAT IHC Expression**

<table>
<thead>
<tr>
<th>Intensity</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>3.5</th>
</tr>
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</table>
| % Steatosis in Liver Tissue | TIP47

Straub, Hepatology 2008;47:1936

Hepatic Steatosis: Role of PAT

- Perilipin: zone 3; small/medium droplets

Perilipin-3
Perilipin-2
Perilipin-1

TIP47
AP
CV
PF
D-PAS

Steatotic human liver

Charlton, Hepatology 2008;47:1936

Other Histologic Markers?

- FABP-1 IHC Expression

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Perilipin
Adipophillin
Adiponectin
FABP-1

* = significant

Charlton, Hepatology 2009;49:2175

- Loss of protective effect of FABP-1
- Role in FA oxidation, lipogenesis, insulin
- New mechanism of FFA lipotoxicity
Other Histologic Markers?

• Early and late NASH... marker
  • Stimulated by oxidative stress
  • Partially mediated by NfκB

Liver Cell Injury: Ballooning

What is Ballooning?
**K8/18 for Ballooning, MDB**

![Immunohistochemical stain for K8/18 showing ballooning in MDB](Feldstein, Gastroenterology 2003; 125:437)

**Apoptosis**

- Markers of apoptosis
- NASH > steatosis = controls (p < .01)
- Correlate with increased fibrosis score, and moderate to severe activity (p < .02)
- Acidophil body index

![Immunohistochemical stain for apoptosis](Feldstein, et al. Hepatology 2009; epub August 2009)

**Apoptosis: Plasma CK18 Fragments**

![Graph showing plasma CK18 levels in different groups](Wieckowska, et al. Hepatology 2006;44:27)

**CK18 Fragments: Plasma Marker to Predict SH**

![Graph showing plasma CK18 levels in different groups](Wieckowska, et al. Hepatology 2006;44:27)

<table>
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<tr>
<th>CK18 Fragment Level Cut-off Value</th>
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<tbody>
<tr>
<td>Validity Measure</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>PPV</td>
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<tr>
<td>NPV</td>
</tr>
<tr>
<td>395 IU/L</td>
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<td>99.9</td>
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<td>85.7</td>
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<td>99.9</td>
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<td>85.7</td>
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<tr>
<td>380.2 IU/L</td>
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<td>94.4</td>
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<td>90.5</td>
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<tr>
<td>95.0</td>
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<tr>
<td>89.5</td>
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</table>
**CK-18 Fragment Levels are Increased in the Liver of Patients with NASH**

- Normal biopsy
- "Not NASH" (Simple Steatosis)
- "Definitive NASH"

NAFLD Activity Score (NAS)

![Images of liver biopsies with NAS scores](image)

**Portal Inflammation**

**Portal Chronic Inflammation**

- Pediatric NAFLD
- Concurrent Disease
  - HCV, other forms of CLD (~5-10%)
- Resolution after treatment
- Severe NAFLD
  - Clinical parameters
  - Histology

![Images of liver biopsies with chronic inflammation](image)

**What are we learning from treatment trials?**

- Pretreatment Bx
- Posttreatment Bx

**Recent Treatment Trials: Primary Histologic Findings**

<table>
<thead>
<tr>
<th>Study</th>
<th>(n)</th>
<th>TX</th>
<th>Post-tx bx (n)</th>
<th>Histologic Findings Reported</th>
</tr>
</thead>
</table>
| Neuschwander-Tetri, et al     | 30  | Rosi        | 22             | 45% no longer NASH; improved grade, steatosis, inflammation, ballooning (p=.004)  
Shift toward increased portal CI (p=.02)  
No change in fibrosis score, shift from dense to delicate perisinusoidal fibrosis (p=.02) |
| Promrat, et al                | 18  | Pio         | 18             | 67% had histologic response, decreased steatosis, ballooning, lobular inflammation, Mallory’s hyaline, fibrosis (p<.05)  
No change in portal inflammation. |
| Kral, et al                   | 689 | BPD         | 104 (re-op)    | Steatosis decreased in all (p < .0001); inflammation gone in 61% of original, developed anew in 10%  
4/10 had “features of HCV”; portal inflammation  
Fibrosis: decreased 28%, increased 42%; no change 34% |
| Dixon, et al                  | 36  | LAGR        | 36             | 83% no longer NASH; significant improvement in steatosis, inflammation, fibrosis (p < .001).  
No change in portal inflammation.  
Fibrosis: Stage ≥ 2: 78% → 13% (p < .001) |
| Barker, et al                 | 149 | RYGB        | 19             | 89% no longer NASH; significant improvement in steatosis, ballooning, lobular inflammation and portal and lobular fibrosis (all p<0.001).  
No change in portal inflammation. |

**Results: Total Cases**

Adults: n = 728  
Pediatrics: n = 205

- Older (p < 0.0001)
- Female gender (p = 0.001)
- Greater BMI (p < 0.0001)
- Elevated serum insulin (p = 0.001)
- Higher HOMA-IR score (p < 0.0001)
- Hx of Medication for NAFLD (p = 0.0004)
- Diabetes (p < 0.0001)
- Hypertension (p < 0.0001)
**Histology Results: NONE v > MILD**

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<tr>
<th>ADULTS</th>
<th>PEDIATRICS</th>
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<td>• Panacinar or azonal steatosis (52% v 20%) (p&lt;0.001)</td>
<td>• Panacinar steatosis (41% v 15%) (p&lt;0.001)</td>
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<tr>
<td>• Ballooning (many &gt; few, none) (60% v 20%) (p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>• Advanced fibrosis (&gt;2) (60% v 4%) (p&lt;0.0001)</td>
<td>• Periportal/portal fibrosis (Stage 1c) (p&lt;0.0001)</td>
</tr>
</tbody>
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**WHAT’S “NEW” IN FIBROSIS?**

- Zone 3 perisinusoidal fibrosis
- Periportal fibrosis, ductular reaction

**Arterialization of Fibrosed Central Zones**

- Ferrell et al (NASH CRN), Hepatology 2007;46:732A

- Brunt, Hepatology 2009;49:409
“Evolution” in Scoring in Metabolic FLD

Descriptive types related to outcome

Types 1-4
Matteoni, 1999

Type 1: Steatosis
Type 2: Steatosis plus inflammation
Type 3: Steatosis plus ballooning
Type 4: Steatosis plus ballooning with Mallory’s and/or fibrosis

Spectrum of NAFLD

“Evolution” in Scoring in Metabolic FLD

Separated Activity, Fibrosis Graded each, as in CH

“Brunt Score” 1999

<table>
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<tr>
<th>Stage</th>
<th>Zone 3, portal- bridging</th>
<th>Partial- bridging</th>
<th>Bridging</th>
<th>Cirrhosis</th>
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<tbody>
<tr>
<td>1</td>
<td>Focal or extensive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>As above</td>
<td>Focal or extensive</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Bridging septa</td>
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</tr>
<tr>
<td>4</td>
<td>+/-</td>
<td>+/-</td>
<td>Extensive</td>
<td>+/-</td>
</tr>
</tbody>
</table>
“Evolution” in Scoring in Metabolic FLD

Created “NAS”, based on aggregate score maintained division of Activity and Fibrosis

Descriptive types related to outcome

Component Scoring for Rx Trials
NIDDK/Kleiner “CRN” 2005

NAS, based on aggregate score maintained division of Activity and Fibrosis

NAFLD Activity Score, NAS (0-8)

Pattern of NAFLD

• Steatosis (0-3)
  • <5%; 5-33%; 33-66%; >66%

• Lobular Inflam (0-3)
  • 0, <2; 2-4; >4 foci/20x

• Ballooning (0-2)
  • None, few, many/prominent

Fibrosis Score (0-4)
Masson’s Trichrome

- 1a, b: Zone 3 PSF
- 1c: Portal only
- 2: Zone 3 + portal/periportal
- 3: Bridging
- 4: Cirrhosis

NAFLD Activity Score: Adults

Dx: Steatohepatitis

% of All Scores

0 1 2 3 4 5 6 7 8

NAS

Modified from Kleiner et al., Hepatology 2005; 41:1313

NAFLD Activity Score

“…note that the primary purpose of the NAS is to assess overall histological change; **it is not intended that numeric values replace the pathologist’s diagnostic determination of steatohepatitis.**”

Kleiner et al. Hepatology 2005; 41:1319
Sunset in the Okavango Delta, Botswana
Challenges in NASH 2009

- Minimum components for diagnosis of SH
- What is ballooning?
- Scoring the lesions

Apoptosis: Plasma Marker

- 44 subjects, suspected “NAFLD”
  - liver biopsy; “CRN” scoring and diagnostic criteria
  - ELISA for caspase-3 generated CK18 fragments in plasma (Bantel et al)
  - IHC confirmation in liver biopsies
    - Caspase-3 cleavage product of CK18


Arterialization of Fibrosed Central Zones

Ferrell et al (NASH CRN), Hepatology 2007;46:732A

p < 0.0001

Concepts of Pathogenesis… NAFLD

Metabolic Syndrome
Fatty Liver Disease

INSULIN RESISTANCE
M > F
Hepatocytes, macrophages
Increased FFA oxidation
Dietary, Hepatic lipid processing
Body habitus

Role of small bowel bacterial overgrowth
Hyperinsulinemia, ↑ glucose,
↑ CTGF, adipose tissue products;
lipid, anapaptosis,
neoproteins

Tinakos and Brunt, in Odze et al, Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas, 2nd ed, 2009
Specimen adequacy...sampling concerns

How good are we?

Understand the disease process(es), nuances in histologic diagnoses
Liver Cell Injury: Ballooning