Steatotic liver disease
Fatty liver disease

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Non-Neoplastic Liver Pathology
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Working Group of Digestive Pathology
Belgian Society of Pathology
OUTLINE

• NAFLD = Non-Alcoholic Fatty Liver Disease
• Steatosis
• Steatohepatitis
• Fibrosis staging in fatty liver disease
• Cryptogenic cirrhosis
• Diagnostic challenges
Steatosis/Steatohepatitis

Most common etiologies

- NAFLD = Non-Alcoholic Fatty Liver Disease

- Excess alcohol
- Drugs
NAFLD and Metabolic Syndrome

NAFLD Chronic liver disease, includes steatosis (NAFL) and steatohepatitis

High incidence – Most adults, but also children and teenagers

<table>
<thead>
<tr>
<th>NAFLD</th>
<th>Related to high incidence of obesity</th>
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<tr>
<td><em>Non-Alcoholic Fatty Liver Disease</em></td>
<td>Affects ~25% of adult population worldwide</td>
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<td><em>23.7%</em> for Europe</td>
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<td></td>
<td>Younossi ZM et al, Hepatology 2016, 64: 73-84</td>
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<table>
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<tr>
<th>NASH</th>
<th>3-16% for Europe</th>
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<tr>
<td><em>Non-Alcoholic SteatoHepatitis</em></td>
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<td>Minervini MI et al, J Hepatol 2009, 50: 501-510</td>
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Metabolic syndrome: 3 or more of the following

- Central obesity
- Elevated fasting serum glucose and insulin resistance
- High triglycerides
- Low HDL cholesterol
- High blood pressure
Steatosis

• Macrovesicular steatosis
• Mixed macro-microvesicular steatosis
  “macro-mediovesicular steatosis”
Steatosis

• Involvement
  • None
  • <5% - Minimal
  • 5-33% - Mild
  • 34-66% - Moderate
  • >66% - Marked

• Scoring best done on low-power lens (4X or 10X)
• Score by percentage of surface area with macro-mediovesicular fat
Grade 1, scale 0-3
Mild

Grade 2, scale 0-3
Moderate

Grade 3, scale 0-3
Marked
Zonation of fat

- Zone 3 distribution (centrilobular)
- Zone 1 distribution (periportal)
- Azonal distribution (randomly scattered) - typically moderate/marked
- Panacinar distribution (diffuse) – typically mild
Dogma within NAFLD spectrum
Steatosis little risk for fibrosis progression
Steatohepatitis much higher risk for fibrosis progression

New insights into natural history of NAFLD
Distinction between NAFL and NASH of limited prognostic value

Patients with fibrosis progression: NASH features on follow-up biopsy
Suggesting that although NASH may not be present in early phases of the disease, it is a necessary pathogenic driver of fibrosis progression

Steatohepatitis

• Steatosis plus active injury

• Active injury
  • Ballooned hepatocytes ± Mallory-Denk bodies
  • Lobular inflammation

Steatosis
Without these histologic findings of active injury
Steatohepatitis

• Steatosis **plus** active injury

• Active injury
  • Ballooned hepatocytes ± Mallory-Denk bodies
  • Lobular inflammation

Controversy
Some authors require balloon cells
Some authors require lobular inflammation
Steatohepatitis

• Steatosis **plus** active injury

• Active injury
  • Ballooned hepatocytes ± Mallory-Denk bodies
  • Lobular inflammation

Reasonable approach in daily practice
Convincing balloon cells and/or
More than trivial lobular inflammation
Ballooned hepatocytes
Ballooned cells

• Hepatocytes that are injured but not yet dead
• Can also be seen in other diseases, e.g. cholestatic liver disease
• In NAFLD most commonly in zone 3
• Often in close proximity to fibrosis

• Large size
• Cytoplasmic clearing
• Eosinophilic clumps and sometimes Mallory hyaline

    Damaged and ubiquitinated cytoskeleton proteins
* In no study set case was there absolute concordance among the nine pathologists for a ballooning score of 1. During the second round of reviews, this case was scored as 1 ballooning injury by 8 of the 9 pathologists.
What causes hepatocyte ballooning

- Oxidative damage to cytoskeleton
- Intermediate filaments K8/18
- Loss of K8/18 in ballooned cells

Lackner C et al, J Hepatol 2008, 48: 821-828
Lobular inflammation is mostly lymphocytic

Neutrophils are not necessary, relatively rare in NAFLD

Except when marked active disease with numerous balloon cells and abundant Mallory hyaline

• ~80% of NASH has mild lobular inflammation
• ~20% of NASH has moderate lobular inflammation
• ~0% has marked lobular inflammation

Should work up for other diseases

Pitfall: surgical hepatitis (wedge biopsies, resections)
Inflammation

Portal inflammation is mostly lymphocytic
  • Mild
  • Can be focally moderate

Portal inflammation: how much is too much
  • Moderate but diffuse portal inflammation
  • Marked portal inflammation
    Should work up for other diseases
Additional findings

Non-essential features in steatohepatitis

• Mallory hyaline in zone 3
• Mild iron deposits in hepatocytes or sinusoidal cells
• Glycogenated nuclei
• Lipogranulomas
• Megamitochondria
• Acidophil bodies (occasional)
• Microvesicular steatosis foci
NAFLD Grading

AASLD and NASH CRN (NASH Clinical Research Network) - INTEGRATED APPROACH

**NAFLD Activity Score - NAS (Brunt/Kleiner score)** - Kleiner DE et al, Hepatology 2005, 41: 1313-1321

Research purposes
- Fat
- Balloon cells
- Inflammation
- Add these to get grade
- Stage fibrosis separately

**FLIP CONSORTIUM - ANALYTICAL APPROACH**

**SAF score** - Bedossa P et al, Hepatology 2012, 5: 1751-1759

Morbidly obese patients
- Steatosis
- Activity
- Fibrosis
- Clear separation of fat from the ongoing injury (balloon cells, inflammation)
**NAS (NAFLD Activity Score) (Brunt/Kleiner score)**

- **FAT score**
  - 0 = <5% - none
  - 1 = 5-33% - mild
  - 2 = 34-66% - moderate
  - 3 = >66% - severe

- **BALLOONED HEPATOCYTE score**
  - 0 = None
  - 1 = Few (rare but definite balloon cells as well as cases that are diagnostically borderline)
  - 2 = Many/Prominent

- **LOBULAR INFLAMMATION score** *(score as average on 20X)*
  - 0 = None
  - 1 = < 2 foci per lobule
  - 2 = 2-4 foci per lobule
  - 3 = >4 foci per lobule

- Add these to get grade: score is up to 8

  *Most* cases diagnosed as steatosis have a total score of ≤2
  *Most* cases diagnosed as steatohepatitis have a total score of ≥5

  Total score 3 or 4 can be either steatosis or steatohepatitis
Remark Bedossa P.

NAS = sum of lesions related to different mechanisms and with different clinical relevance (steatosis vs hepatocellular injury)

SAF score (Steatosis-Activity-Fibrosis)

- **Steatosis (0-3) as for NAS CRN**
- **ACTIVITY (0-4) = BALLOONING (0-2) + LOBULAR INFLAMMATION (0-2)**
  
  0= None  
  1= Few, size nl. hepatocyte  
  2= Many, 2X size nl. hepatocyte  
  0= None  
  1= ≤ 2 foci per 20X field  
  2= > 2 foci per 20X field  
- **Fibrosis (0-4) as for NAS CRN**
  
  SO-3A0-4F0-3
The FLIP algorithm

The definition of NASH by an association of 3 features and a clear definition of each of them makes the diagnosis of NASH strongly reproducible.

HEPATOCELLULAR BALLOONING the hallmark of NASH
SHAPE + COLOR + SIZE

LOBULAR INFLAMMATION

Fibrosis staging

• Major prognostic factor

Fibrosis

NAS staging system

• F0 = No fibrosis
• F1 = Pericellular or portal fibrosis (but not both)
  • F1A = Mild pericellular fibrosis (only seen on siriusred/trichrome stain)
  • F1B = Moderate pericellular fibrosis (readily seen on HE)
  • F1C = Only portal fibrosis with no pericellular fibrosis
• F2 = Both pericellular (any) and portal fibrosis (any)
• F3 = Bridging fibrosis
• F4 = Cirrhosis
Fibrosis

NAS staging system

- F0 = No fibrosis
- F1 = Pericellular or portal fibrosis (but not both)
  - F1A = Mild pericellular fibrosis (only seen on siriusred/trichrome stain)
  - F2A = Moderate pericellular fibrosis (readily seen on HE)
  - F1C = Only portal fibrosis with no pericellular fibrosis
- F2 = Both pericellular (any) and portal fibrosis (any)
- F3 = Bridging fibrosis
- F4 = Cirrhosis

Portal fibrosis does not mean there is another disease
Cirrhosis with steatosis and/or ballooned hepatocytes

Cirrhosis with histologic features of NAFLD best considered NASH cirrhosis. Some cases may show residual pericellular fibrosis

“Burnt out NASH cirrhosis”

• Typical steatohepatitis features, including fat, regress with progression of fibrosis and may be lost with cirrhosis

• Many cases labelled as cryptogenic cirrhosis; since this population has a high incidence of type 2 DM, NASH is considered to be the most likely etiology

• Rule out other etiologies and correlate with NASH risk factors
Diagnostic challenges
**Alcoholic steatohepatitis**

Can not be definitively distinguished from NASH by histology

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<tr>
<td>Steatosis</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Ballooned hepatocytes</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Lobular inflammation</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Mallory hyaline</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Neutrophil infiltrate</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>+/-</td>
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<tr>
<td>Obliterated CV</td>
<td>+/-</td>
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Drug induced steatohepatitis

Histological changes identical to NASH have been identified in patients without NASH risk factors exposed to certain drugs

- Amiodarone
- Irinotecan
- Methotrexate
- Perhexiline Maleate
- Tamoxifen
- Steroids
- Estrogen
Metabolic disorders

Wilson disease

Steatosis (non-zonal), glycogenated nuclei, Mallory hyaline in periportal hepatocytes, swollen hepatocytes, portal inflammation, and fibrosis
Microvesicular steatosis

- **Pure** microvesicular steatosis *does not occur in NASH* and indicates severe mitochondrial injury
  - Reye syndrome - salicylates
  - Acute fatty liver of pregnancy
  - Drug (cocaína, tetracycline, antiretrovirals, valproate)
  - Rare genetic disorders
  - Alcoholic foamy degeneration

- Many NAFLD cases will have *minor component* of microvesicular fat
SUMMARY

STEATOHEPATITIS

• Most are NASH or alcohol-related
• Steatosis = Fat (no other injury)
• Steatohepatitis = Fat + Liver injury

  Balloon cells/Lobular inflammation

• Distinctive pattern of fibrosis with pericellular fibrosis
Thank you for your attention